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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D | A2

(11) International Publication Number: **WO 00/26185**

(43) International Publication Date: 11 May 2000 (11.05.00)

(21) International Application Number: PCT/US99/25592

(22) International Filing Date: 29 October 1999 (29.10.99)

(30) Priority Data:
09/183,422 30 October 1998 (30.10.98) US

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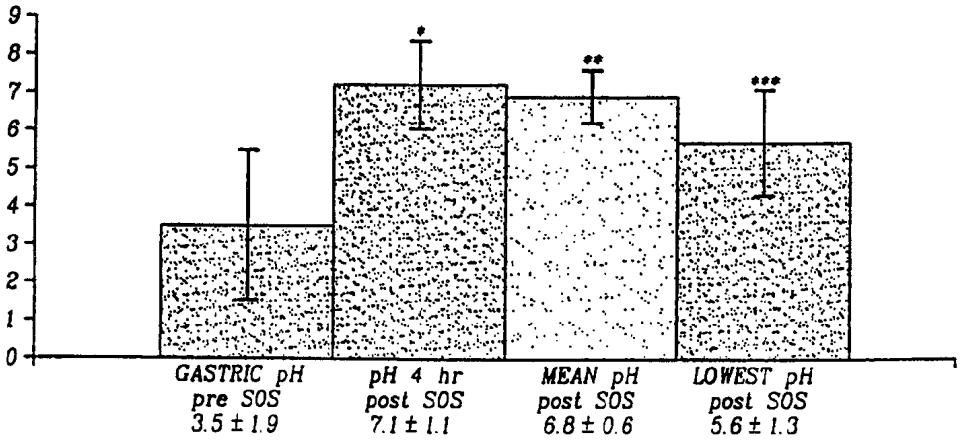
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: OMEPRAZOLE SOLUTION AND METHOD OF USING SAME



(57) Abstract

A method of treating gastric acid disorders by administering to a patient a pharmaceutical composition including a proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal where the administering step consists of a single dosage form without requiring further administering of the bicarbonate salt of the Group IA metal. A pharmaceutical composition includes a dry formulation of a proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal. A pharmaceutical composition for making a dry formulation of a proton pump inhibitor which includes a proton pump inhibitor and a bicarbonate salt of a Group IA metal in a form for convenient storage, whereby when the composition is in a dry formulation which is suitable for enteral administration.

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OMEPRAZOLE SOLUTION AND METHOD OF USING SAME

This application is a continuation-in-part of United States Serial Number 08/680,376 filed on January 4, 1996.

TECHNICAL FIELD

The present invention relates to a pharmaceutical preparation containing a substituted benzimidazole, more specifically known as proton pump inhibitor(s) (ppi). More particularly, the present invention relates to a substituted benzimidazole solution/suspension suitable for oral administration.

BACKGROUND OF THE INVENTION

Omeprazole is a substituted benzimidazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole, that inhibits gastric acid secretion. Omeprazole belongs to a class of antisecretory compounds, the proton pump inhibitor that do not exhibit anti-cholinergic or H_2 histamine antagonist properties. Drugs of this class suppress gastric acid secretion by the specific inhibition of the H^+/K^+ ATPase enzyme system (proton pump) at the secretory surface of the gastric parietal cell.

Typically, omeprazole and lansoprazole or other proton pump inhibitors in the form of a delayed-release capsule, is prescribed for short-term treatment of active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison syndrome. These conditions are

caused by an imbalance between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors.

These above-listed conditions commonly arise in healthy or critically ill patients and may be accompanied by significant upper gastrointestinal bleeding. H_2 antagonists, antacids, and sucralfate are commonly administered to minimize the pain and the complications related to these conditions. These drugs have certain disadvantages associated with their use. Some of these drugs are not completely effective in the treatment of the aforementioned conditions and/or produce adverse side effects, such as mental confusion, constipation, diarrhea, thrombocytopenia,(lowered platelet count) and/or are relatively costly modes of therapy as they require the use of automated infusion pumps for continuous intravenous delivery.

Patients with significant physiologic stress are at risk for stress-related gastric mucosal damage and subsequent upper gastrointestinal bleeding (Marrone and Silen, 1984). Risk factors that have been clearly associated with the development of stress-related mucosal damage are mechanical ventilation, coagulopathy, extensive burns, head injury, and organ transplant (Zinner et al., 1981; Larson et al., 1984; Czaja et al., 1974; Skillman et al., 1969; and Cook et al., 1994). One or more of these factors are often found in critically ill, intensive care unit patients. A recent cohort study challenges other risk

factors previously identified such as acid-base disorders, multiple trauma, significant hypertension, major surgery, multiple operative procedures, acute renal failure, sepsis, and coma (Cook et al., 1994). Regardless of the risk type, stress-related mucosal damage results in significant morbidity and mortality. Clinically significant bleeding occurs in at least twenty percent of patients with one or more risk factors who are left untreated (Martin et al., 1993). Of those who bleed, approximately ten percent require surgery (usually gastrectomy) with a reported mortality of thirty percent to fifty percent (Czaja et al., 1974; Peura and Johnson, 1985). Those who do not need surgery often require multiple transfusions and prolonged hospitalization. Prevention of stress-related upper gastrointestinal bleeding is an important clinical goal.

In addition to general supportive care, the use of drugs to prevent stress-related mucosal damage is considered by many to be the standard of care (AMA Drug Evaluations). However, general consensus is lacking about which drugs to use in this setting (Martin et al., 1993; Gafter et al., 1989; Martin et al., 1992). In two recent meta-analyses (Cook et al., 1991; Tryba, 1994), antacids, sucralfate, and H_2-antagonists were all found to be superior to placebo and similar to one another in preventing upper gastrointestinal bleeding. Yet, prophylactic agents are withdrawn in fifteen to twenty percent of patients in which they are employed because of failure to prevent bleeding, or control pH (Ostro et al.,

1985; Siepler, 1986; Ballesteros et al., 1990), or because of adverse effects (Gafter et al., 1989; Sax, 1987; Vial et al., 1991; Cantu and Korek, 1991; Spychal and Wickham, 1985). In addition, the characteristics of an ideal agent for the prophylaxis of stress gastritis and concluded that none of the agents currently in use fulfill their criteria (Smythe and Zarowitz, 1994).

Omeprazole and lansoprazole and the other proton pump inhibitors reduce gastric acid production by irreversibly inhibiting the H+/K+ ATPase of the parietal cell - the final common pathway for gastric acid secretion (Fellenius et al., 1981; Wallmark et al., 1985; Frylund et al., 1988). Because this drug maintains gastric pH control throughout the dosing interval and has a very good safety profile, it is a logical choice for stress ulcer prophylaxis. The absence of an intravenous or oral liquid dosage form in the United States, however, has limited the testing and use of omeprazole in the critical care patient population. Subsequently, Barie et al. (Barie and Hariri, 1992) described the use of omeprazole enteric-coated pellets administered through a nasogastric tube to control gastrointestinal hemorrhage in a critical care patient with multi-organ failure.

Stress ulcer prophylaxis has become routine therapy in intensive care units in most hospitals (Fabian et al, 1993.; Cook et al., 1991). Controversy remains regarding pharmacologic intervention to prevent stress-related bleeding in critical care patients. It has been suggested

that the incidence and risk of gastrointestinal bleeding has decreased in the last ten years and drug therapy may no longer be needed (Cook et al., 1994; Tryba, 1994; Schepp, 1993). This reasoning is not supported by a recent placebo-controlled study. Martin et al. conducted a prospective, randomized, double-blind, placebo-controlled comparison of continuous-infusion cimetidine and placebo for the prophylaxis of stress-related mucosal damage (Marten et al., 1993). The study was terminated early because of excessive bleeding-related mortality in the placebo group. It appears that the natural course of stress-related mucosal damage in a patient at risk who receives no prophylaxis remains significant. In the placebo group, thirty-three percent of patients developed clinically significant bleeding, nine percent required transfusion, and six percent died due to bleeding-related complications. In comparison, fourteen percent of cimetidine-treated patients developed clinically significant bleeding, six percent required transfusions, and 1.5% died due to bleeding-related complication; the difference in bleeding rates between treatment groups was statistically significant. This study clearly demonstrated that continuous-infusion cimetidine reduced morbidity in critical care patients. Although, these data were used to support the approval of continuous-infusion cimetidine by the Food and Drug Administration for stress ulcer prophylaxis, H_2-antagonists fall short of being the optimal pharmacotherapeutic agents for preventing of stress-related mucosal bleeding.

Another controversy surrounding stress ulcer prophylaxis is which drug to use. In addition to the various H_2-antagonists, antacids and sucralfate are other treatment options for the prophylaxis of stress-related mucosal damage. An ideal drug in this setting should possess the following characteristics: prevent stress ulcers and their complications, be devoid of toxicity, lack drug interactions, be selective, have minimal associated costs (such as personnel time and materials), and be easy to administer (Smythe and Zarowitz, 1994).

Some have suggested that sucralfate is possibly the ideal agent for stress ulcer prophylaxis (Smythe and Zarowitz, 1994). Randomized, controlled studies support the use of sucralfate (Borrero et al., 1986; Tryba, 1987; Cioffi et al., 1994; Driks et al., 1987), but data on critical care patients with head injury, trauma, or burns are limited. In addition, a recent study comparing sucralfate and cimetidine plus antacids for stress ulcer prophylaxis reported clinically significant bleeding in three of forty-eight (6%) sucralfate-treated patients, one of whom required a gastrectomy (Cioffi et al., 1994). In the study performed by Driks and coworkers that compared sucralfate to conventional therapy (H_2-antagonists, antacids, or H_2-antagonists plus antacids), the only patient whose death was attributed to stress-related upper gastrointestinal bleeding was in the sucralfate arm (Driks et al., 1987).

H_2-antagonists fulfill many of the criteria for an ideal stress ulcer prophylaxis drug. Yet, clinically significant bleeds can occur during H_2-antagonist prophylaxis (Martin et al., 1993; Cook et al., 1991; Schuman et al., 1987) and adverse events are not uncommon in the critical care population (Gafter et al., 1989; Sax, 1987, Vial et al., 1991; Cantu and Korek, 1991; Spychal and Wickham, 1985). One reason proposed for the therapeutic H_2-antagonist failures is lack of pH control throughout the treatment period (Ostro et al., 1985). Although the precise pathophysiologic mechanism(s) involved in stress ulceration are not clearly established, the high concentration of hydrogen ions in the mucosa (Fiddian-Green et al., 1987) or gastric fluid in contact with mucosal cells appears to be an important factor. A gastric pH > 3.5 has been associated with a lower incidence of stress-related mucosal damage and bleeding (Larson et al., 1984; Skillman et al., 1969; Skillman et al., 1970; Priebe and Skillman, 1981). Several studies have shown that H_2-antagonists, even in maximal doses, do not reliably or continuously increase intragastric pH above commonly targeted levels (3.5 to 4.5). This is true especially when used in fixed-dose bolus regimens (Ostro, 1985; Siepler, 1986; Ballesteros et al., 1990). In addition, gastric pH levels tend to trend downward with time when using a continuous-infusion of H_2-antagonists, which may be the result of tachyphylaxis (Ostro et al., 1985; Wilder-Smith and Merki, 1992).

Because stress ulcer prophylaxis is frequently employed in the intensive care unit, it is essential from both a clinical and economic standpoint to optimize the pharmacotherapeutic approach. In an attempt to identify optimal therapy, cost of care becomes an issue. All treatment costs should be considered, including the costs of treatment failures and drug-related adverse events. While the actual number of failures resulting in mortality is low, morbidity (e.g., bleeding that requires blood transfusion) can be high, even though its association with the failure of a specific drug is often unrecognized.

Proton pump inhibitors such as omeprazole represent an advantageous alternative to the use of H_2 antagonists, antacids, and sucralfate as a treatment for complications related to stress-related mucosal damage. However, in their current form (capsules containing an enteric-coated granule formulation of proton pump inhibitor), proton pump inhibitors can be difficult or impossible to administer to patients who are unable (critically ill patients, children, elderly, patients suffering from dysphagia) or patients who are either unwilling or unable to swallow tablets or capsules. Therefore, it would be desirable to formulate a proton pump inhibitor solution or suspension which can be enterally delivered to a patient thereby providing the benefits of the proton pump inhibitor without the drawbacks of the current capsule dose form.

Omeprazole, the first proton pump inhibitor introduced into use, has been formulated in many different embodiments

such as in a mixture of polyethylene glycols formed a mixture of adeps solidus and sodium lauryl sulfate in a soluble, basic amino acid to yield a formulation designed for administration in the rectum as shown in United States Patent No. 5,219,870 to Kim.

United States Patent No. 5,395,323 to Berglund ('323) discloses a device for mixing a pharmaceutical from a solid supply into a parenterally acceptable liquid form for parenteral administration to a patient. The '323 patent teaches the use of an omeprazole tablet which is placed in the device and dissolved by normal saline, and infused into the patient. This device and method of infusing omeprazole does not provide the omeprazole solution as an enteral product nor is this omeprazole solution directly administered to the diseased or affected areas, namely the stomach and upper gastrointestinal tract, nor does this omeprazole formulation provide the immediate anti-acid effect of the present formulation.

United States Patent No. 4,786,505 to Lovgren et al., discloses a pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as a core material in a tablet formulation. The use of the alkaline material, which can be chosen from such substances as the sodium salt of carbonic acid, are used to form a "micro-pH" around each omeprazole particle to protect the omeprazole which is highly sensitive to acid pH. The powder mixture is then

formulated to small beads, pellets, tablets and may be loaded into capsules by conventional pharmaceutical procedures.

This formulation of omeprazole does not provide an omeprazole dose form which can be enterally administered to a patient who may be unable and/or unwilling to swallow capsules or pellets nor does it teach a convenient form which can be used to make an omeprazole or other proton pump inhibitor solution or suspension.

Several buffered omeprazole solutions have been disclosed. Andersson et al., 1993; Landahl et al., 1992; Andersson et al., 1990; Regardh et al., 1990; Andersson et al., 1990; Pilbrant et al., 1985.

All of the buffered omeprazole solutions described in these references were administered orally and were given to healthy subjects who were able to ingest the oral dose. In all of these studies, omeprazole was suspended in a solution including sodium bicarbonate, as a pH buffer, in order to protect the acid sensitive omeprazole during administration.

In all of these studies, repeated administration of sodium bicarbonate both prior to, during, and following omeprazole administration were required in order to prevent acid degradation of the omeprazole given via the oral route of administration. As a result, the ingestion of the large amounts of sodium bicarbonate and large volumes of water were required. In the above-cited studies, as much as 48

mmoles of sodium bicarbonate in 300 ml of water must be ingested for a single dose of omeprazole to be orally administered.

Initial reports of increased frequency of pneumonia in patients receiving stress ulcer prophylaxis with agents that raise gastric pH has influenced the pharmacotherapeutic approach to management of critical care patients. However, several recent studies (Simms et al., 1991; Pickworth et al., 1993; Ryan et al., 1993; Fabian et al., 1993), a meta-analysis (Cook et al., 1991), and a closer examination of the studies that initiated the elevated pH-associated pneumonia hypotheses (Schepp, 1993) cast doubt on a causal relationship. The relationship between pneumonia and antacid therapy is much stronger than for H_2-antagonists. The shared effect of antacids and H_2-antagonists on gastric pH seems an irresistible common cause explanation for nosocomial pneumonia observed during stress ulcer prophylaxis. However, there are important differences between these agents that are not often emphasized (Laggner et al., 1989). When antacids are exclusively used to control pH in the prophylaxis of stress-related upper gastrointestinal bleeding, large volumes are needed. Volume, with or without subsequent reflux, may be the underlying mechanism(s) promoting the development of pneumonia in susceptible patient populations rather than the increased gastric pH. The rate of pneumonia in our study (12%) was not unexpected in this critical care population and compares with sucralfate,

which does not significantly raise gastric pH (Pickworth et al., 1993; Ryan et al., 1993).

The buffered omeprazole solutions of the above cited prior art require large amounts of sodium bicarbonate to be given by repeated administration. This is necessary to prevent acid degradation of the omeprazole. The administration of large amounts of sodium bicarbonate can produce at least four significant adverse effects which can dramatically reduce the efficacy of the omeprazole in patients and reduce the overall health of the patients. In the above-cited studies, basically healthy volunteers rather than sick patients were given only one or two dosages of omeprazole utilizing pre-dosing and post-dosing with large volumes of sodium bicarbonate. This dosing protocol would not be suitable for sick or critically ill patients who must receive multiple doses of omeprazole.

Since bicarbonate is usually neutralized in the stomach or is absorbed, such that belching results, patients with gastroesophageal reflux may exacerbate or worsen their gastroesophageal reflux disease as the belching can cause upward movement of stomach acid (Brunton, 1990).

Patients with conditions, such as hypertension or heart failure, are standardly advised to avoid the intake of excessive sodium as this can cause aggravation or exacerbation of their hypertensive conditions (Brunton, 1990).

Additionally, patients with numerous conditions which typically accompany critical illness should avoid the intake of excessive sodium bicarbonate as it can cause metabolic alkalosis which can result in a serious worsening of the patient's condition. Furthermore, excessive antacid intake (such as sodium bicarbonate) can result in drug interactions which produce serious adverse effects. For example, by altering gastric and urinary pH, antacids can alter rates of drug dissolution and absorption, bioavailability, and renal elimination (Brunton, 1990).

Since buffered omeprazole solution requires prolonged administration of the antacid, sodium bicarbonate, it makes it difficult for patients to comply with the above recommendation.

In addition to the disadvantages associated with excessive intake of sodium bicarbonate, the above-cited prior art teaches a relatively complex regimen for the oral administration of omeprazole. For example, in the Pilbrant et al. (1985) reference, the oral omeprazole administration protocol calls for administering to a subject who has been fasting for at least ten hours, a solution of 8 mmoles of sodium bicarbonate in 50 ml of water. Five minutes later, the subject ingests a suspension of 60 mg of omeprazole in 50 ml of water which also contains 8 mmoles of sodium bicarbonate. This is rinsed down with another 50 ml of 8 mmoles sodium bicarbonate solution. Ten minutes after the ingestion of the omeprazole dose, the subject ingests 50 ml of bicarbonate solution (8 mmoles). This is repeated at

twenty minutes and thirty minutes post omeprazole dosing to yield a total of 48 mmoles of sodium bicarbonate and 300 ml of water in total which are ingested by the subject for a single omeprazole dose.

Not only does this regimen require the ingestion of excessive amounts of bicarbonate and water, it is unlikely that a healthy patient would comply with this regimen for each dose of omeprazole over the course of a prescribed omeprazole protocol. It is unlikely or even improbable that a critically ill patient would be able to comply with this regimen.

Even in healthy patients, the complexity of the drug regimen leads to the conclusion that patients would be unlikely to comply with this regimen thereby leading to a lack of beneficial outcome for the patient. It is well documented that patients who are required to follow complex schedules for drug administration are non-compliant and, thus, the efficacy of the buffered omeprazole solutions of the prior art would be expected to be reduced due to non-compliance. Compliance has been found to be markedly reduced when patients are required to deviate from a schedule of one or two (usually morning and night) doses of a medication per day. The use of the prior art buffered omeprazole solutions which require administration protocols with numerous steps, different drugs (sodium bicarbonate + omeprazole + PEG400 versus sodium bicarbonate alone), and specific time allotments between each stage of the total omeprazole regimen in order to achieve efficacious results

is clearly in contrast with both current drug compliance theories and human nature.

The prior art (Pilbrant et al., 1985) teaches that the buffered omeprazole suspension can be stored at refrigerator temperatures for a week and deep frozen for a year while still maintaining 99% of their initial potency. It would be desirable to have an omeprazole or other proton pump inhibitor solution or suspension which could be stored at room temperature or in a refrigerator for periods of time which exceed those of the prior art while still maintaining 99% of the initial potency. Additionally, it would be advantageous to have a form of the omeprazole and bicarbonate which can be utilized to instantly make the omeprazole solution/suspension of the present invention which is supplied in a solid form which imparts the advantages of improved shelf-life at room temperature, lower cost to produce, less expensive shipping costs, and which is less expensive to store.

The present invention provides a solution/suspension of proton pump inhibitors such as omeprazole, lansoprazole or other proton pump inhibitor (pantoprazole, rabeprazole, dontoprazole, habeprozole, perprazole or other proton pump inhibitor) which is suitable for administration which includes all of the aforementioned advantages.

It would, therefore, be desirable to have an proton pump inhibitor formulation which provides a cost effective means for the treatment of the aforementioned conditions

without the adverse effect profile of H_2 receptor antagonist, antacids, and sucralfate. Further, it would be desirable to have a proton pump inhibitor formulation which is convenient to prepare and administer to patients unable to ingest capsules, which is rapidly absorbed, can be orally or enterally delivered as a liquid form or solid form which becomes a liquid in the stomach or upper GI tract (the desired treatment regimen.). It is desirable that the liquid formulation not clog indwelling tubes, such as nasogastric tubes or other similar tubes, and which acts as an antacid immediately upon delivery. Furthermore, it would be desirable to have a pharmaceutical composition which is highly efficacious for the treatment of the aforementioned conditions.

SUMMARY OF THE INVENTION AND ADVANTAGES

In accordance with the present invention, there is provided a method of treating gastric acid disorders by administering to a patient a pharmaceutical composition including a proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal where the administering step consists of a single dosage form without requiring further administering of the bicarbonate salt of the Group IA metal.

The present invention further provides a pharmaceutical composition includes a dry formulation of a proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal.

The present invention further provides a phannaceutical composition for making a dry formulation of a proton pump inhibitor which includes a proton pump inhibitor and a bicarbonate salt of a Group IA metal in a form for convenient storage, whereby the composition is in a dry formulation which is suitable for enteral administration.

BRIEF DESCRIPTION OF THE DRAWINGS

Other advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawing wherein:

Figure 1 is a graph showing the effect of the omeprazole solution/suspension of the present invention on gastric pH in patients at risk for upper gastrointestinal bleeding from stress-related mucosal damage;

Figure 2 is a flow chart illustrating a patient enrollment scheme;

Figure 3 is a bar graph illustrating gastric pH both pre- and post-administration of omeprazole solution/suspension according to the present invention; and

Figure 4 is a graph illustrating the stomach pH values of both chocolate plus lansoprazole in powder form and lansoprazole alone.

DETAILED DESCRIPTION OF THE INVENTION

A pharmaceutical composition which can include an aqueous solution/suspension, or dry formulation, of proton pump inhibitors, such as omeprazole or other substituted benzimidazoles which are proton pump inhibitors such as lansoprazole, pantoprazole, rabeprazole, dontroprazole, perprazole, habeprazole, and derivatives thereof in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal is disclosed. For the purposes of description, the composition includes dry formulations, solutions and/or suspensions of the omeprazole or other proton pump inhibitors. Hereinafter, the use of the term "solution" includes solutions and/or suspensions of the substituted benzimidazoles.

The pharmaceutical composition of the present invention is prepared by mixing omeprazole (Merck & Co. Inc., West Point, PA) or other proton pump inhibitors or derivatives thereof with a solution including a bicarbonate salt of a Group IA metal. Preferably, omeprazole or other proton pump inhibitor powder or granules, which can be obtained from a capsule, are mixed with a sodium bicarbonate solution to achieve a desired final omeprazole concentration. As an example, the concentration of omeprazole in the solution/suspension can range from approximately 0.5 mg/ml to approximately 6.0 mg/ml. The preferred concentration for the omeprazole in the solution/suspension ranges from approximately 1.0 mg/ml to

approximately 4.0 mg/ml with 2mg/ml being the standard concentration.

The pharmaceutically effective carrier includes the bicarbonate salt of the Group IA metal and can be prepared by mixing the bicarbonate salt of the Group IA metal, preferably sodium bicarbonate, with water. The concentration of the bicarbonate salt of the Group IA metal in the composition generally ranges from approximately 5.0 percent to approximately 60.0 percent. Preferably, the concentration of the bicarbonate salt of the Group IA metal ranges from approximately 7.5 percent to approximately 10.0 percent. In a preferred embodiment of the present invention, sodium bicarbonate is the preferred salt of the Group IA metal and is present in a concentration of approximately 8.4 percent.

In a preferred embodiment of the present invention, specific example of the enterically-coated omeprazole particles are obtained from delayed release capsules (Astra Merck) alternatively omeprazole powder can be used. The coated omeprazole particles are mixed with a sodium bicarbonate ($NaHC0_3$) solution which dissolves the enteric coating and forms an omeprazole solution/suspension in accordance with the present invention. The omeprazole solution/suspension has significant pharmacokinetic advantages over standard time-release omeprazole capsules including: a decreased drug absorbance time (-10 to 12 minutes) following administration for the omeprazole solution versus (-2-3 hours) following administration for

the enteric coated pellets; the $NaHCO_3$ solution protects the omeprazole from acid degradation prior to absorption; the $NaHCO_3$ acts as an antacid while the omeprazole is being absorbed; and the solution/suspension can be administered through an existing indwelling tube without clogging, for example, nasogastric or other feeding tubes (jejunal or duodenal) including small bore needle catheter feeding tubes.

As stated above, other proton pump inhibitors can be substituted for the omeprazole or lansoprazole, or other suitable substituted benzimidazoles without departing from the spirit of the present invention. These proton pump inhibitors can include, but are not limited to, lansoprazole, pantoprazole, rabeprazole, dontoprazole, perprazole, habeprazole and other proton pump or acid pump inhibitors. Proton pump inhibitors are membrane impermeable and form disulfide covalent bonds with cysteine residues in the alpha subunit which inhibit the activity of the acid secreting pump. The data presented provides a factual basis for suggesting the use of this group of proton pump inhibitor compounds in accordance with the present invention.

The pharmaceutical composition including the proton pump inhibitors such as omeprazole or lansoprazole or other proton pump inhibitors and derivatives thereof in a pharmaceutically acceptable carrier of a bicarbonate salt of Group IA metal can be used for the treatment of gastrointestinal conditions including, but not limited to,

active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison Syndrome. These conditions are caused by imbalances between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors. Treatment of these conditions is accomplished by administering to a patient an effective amount of the pharmaceutical composition according to the present invention.

The proton pump inhibitor is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners. The "effective amount" for purposes herein thus determine by such considerations as are known in the art. The amount must be effective to achieve improvement, including but not limited to, raising of gastric pH, reduced gastrointestinal bleeding, reduction in the need for blood transfusion, improved survival rate, more rapid recovery, or improvement or elimination of systems and other indicators as are selected as appropriate measures by those skilled in the art.

The dosage range of omeprazole or other proton pump inhibitors such as substituted benzimidazoles and derivatives thereof can range from approximately 2 mg/day

to approximately 100 mg/day. The standard daily dosage is typically 20 mg omeprazole in 10 ml of solution.

In the method of the present invention, the omeprazole solution suspension can be administered in various ways. It should be noted that the omeprazole solution/suspension can be administered as the compound or as the pharmaceutically acceptable salt form (dry) and can be administered alone or in combination with pharmaceutically acceptable carriers. The compounds can be administered orally or enterally. The formulations can be made more palatable by adding flavorings such as chocolate, root beer, and others.

Additionally, various additives including ambicin which enhance the stability, sterility, and isotonicity of the compositions. Additionally, antimicrobial preservatives, antioxidants, chelating agents, and buffers can be added. However, microbiological evidence shows that this formulation inherently possesses anti-microbial activity. Prevention of the action of microorganisms can be enhanced by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like.

In many cases, it would be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Additionally, thickening agents, such as methyl cellulose, are desirable to use in order to reduce settling the omeprazole or derivatives thereof from the suspension.

Furthermore, the use of flavoring agents such as chocolate or chelating agents such as calcium have been shown to act as a potentiator or enhancer of the pharmacologic activity of the proton pump inhibitor as is shown in Figure 4. More specifically, Figure 4 shows that the gastric pH, after 18 hours, of the lansoprazole alone was approximately 1.5, whereas the lansoprazole with the chocolate was approximately 2.9. Therefore the combination of the lansoprazole with chocolate enhanced the pharmacologic activity of the lansoprazole. By measuring the serum gastrin the results establish that the sodium bicarbonate as well as chocolate flavoring and calcium were all able to stimulate the activation of the proton pumps, perhaps due to the release of gastrin. Proton pump inhibitors work by functionally inhibiting the proton pump and can only block activated proton pumps. By further administering the proton pump inhibitor with one of these potentiators or enhancers, there is a synchronization of activation of the proton pump with the absorption of the proton pump inhibitor. This combination produced a much longer pharmacologic effect than when the proton pump inhibitor was administered alone.

The formulations of the present invention can also be manufactured in a concentrated form, such as an effervescent tablet or powder, so that upon reaction with water, the aqueous form of the present invention would be produced for oral or enteral administration.

Additionally, the present invention can be manufactured by utilizing micronized compounds in place of the granules or powder. This process is known as micronization and is utilized in order to produce a particle having a greater diameter. Micronization is the process by which solid drug particles are reduced in size. Since the dissolution rate is directly proportional to the surface area of the solid, and reducing the particle size increases the surface area, reducing the particle size increases the dissolution rate.

Although micronization results in increased surface area causing particle aggregation, which can negate the benefit of micronization and is an expensive manufacturing step, it does have the significant benefit of increasing the dissolution rate of relatively water insoluble drugs, such as omeprazole and other proton pump inhibitors.

A pharmacological formulation of the proton pump inhibitors utilized in the present invention can be administered orally to the patient. A pharmacological formulation of the omeprazole solution/suspension utilized in the present invention is preferably administered enterally. This can be accomplished, for example, by administering the solution/suspension via a nasogastric tube or other indwelling tubes. In order to avoid the critical disadvantages associated with administering large amounts of sodium bicarbonate, the omeprazole solution of the present invention is administered in a single dose which does not require any further administration of

bicarbonate following the administration of the omeprazole solution. That is, unlike the prior art omeprazole solutions and administration protocols outlined above, the formulation of the present invention is given in a single dose which does not require administration of bicarbonate either before administration of the omeprazole or after administration of the omeprazole. The present invention eliminates the need to pre-or post-dose with additional volumes of water and sodium bicarbonate. The amount of bicarbonate administered via the single dose administration of the present invention is less than the amount of bicarbonate administered as taught in the prior art references cited above.

The amount of sodium bicarbonate used in the solution/suspension of the present invention is approximately 1 meq (or mmole) sodium bicarbonate per 2 mg omeprazole, with a range of approximately 0.75 meq (mmole) to 1.5 meq (mmole) per 2 mg of omeprazole.

The present invention further includes a pharmaceutical composition for making a solution/suspension of proton pump inhibitors, which consists essentially of omeprazole or other proton pump inhibitors and derivatives thereof and a bicarbonate salt of a Group IA metal in a form convenient for storage, whereby when the composition is placed into an aqueous solution, the composition dissolves yielding a solution/suspension suitable for enteral administration to a subject. The pharmaceutical composition is in a solid form prior to dissolution in the

aqueous solution. The omeprazole or other substituted benzimidazoles and derivatives thereof and bicarbonate can be formed into a tablet, capsules, or granules, by methods well known to those skilled in the art.

The pharmaceutical composition suitable for making a solution/suspension according to the present invention can further include an effervescing agent to aid in the dissolution of the pharmaceutical composition in the aqueous solution. In the present invention the effervescing agent is sodium bicarbonate.

The resultant omeprazole solution is stable at room temperature for several weeks and inhibits the growth of bacteria or fungi as shown in Example IV below. By providing a pharmaceutical composition including the omeprazole or other substituted benzimidazole and derivatives thereof with bicarbonate in a solid form, which is dissolved in a prescribed amount of aqueous solution to yield the desired concentration of omeprazole and bicarbonate, the cost of production, shipping, and storage are greatly reduced as no liquids are shipped (reducing weight and cost) and there is no need to refrigerate the solid form of the composition or the solution. The resultant solution, can be formulated and then used to provide dosages for a single patient over a course of time or for several patients.

The solid formulation of the present invention could be in the form of a powder, a tablet, a capsule, or other

suitable solid dosage form (e.g. a pelleted form or an effervescing tablet or powder). The solid formulation would then create the present invention when acted upon by a suitable vehicle, for example water. The water may be added either prior to ingestion or the dry formulation may be ingested first and then acted upon by the water utilized to swallow the solid formulation. A third mechanism enables water in the stomach secretions to produce the present invention.

The following experimental data illustrate the utility of the pharmaceutical composition of the present invention.

METHODS

Example I

Patients were evaluable if they met the following criteria: had two or more risk factors for SRMD (mechanical ventilation, head injury, severe burn, sepsis, multiple trauma, adult respiratory distress syndrome, major surgery, acute renal failure, multiple operative procedures, coagulatherapy, significant hypotension, acid-base disorder, and hepatic failure), gastric pH of :≤ 4 prior to study entry, and no concomitant prophylaxis for SRMD.

Nasogastric (ng) tubes were placed in the patients and an omeprazole dosage protocol of 40 mg omeprazole solution/suspension followed by 40 mg omeprazole solution/suspension in eight hours, then 20 mg omeprazole solution/suspension per day, for five days. After each

omeprazole solution/suspension administration, nasogastric suction was turned off for thirty minutes.

Results:

Eleven patients were evaluable. All patients were mechanically ventilated. Two hours after the initial dose of omeprazole solution/suspension 40 mg omeprazole, all patients had an increase in gastric pH to greater than eight as shown in Figure 1. Ten of the eleven patients maintained a gastric pH of greater than or equal to four on 20 mg omeprazole solution/suspension. One patient required 40 mg omeprazole solution/suspension per day (closed head injury, five total risk factors for SRMD). Two patients were changed to omeprazole solution/suspension after having developed clinically significant upper gastrointestinal bleeding while receiving conventional intravenous H_2 antagonists. Bleeding subsided in both cases after twenty-four hours. Clinically significant upper gastrointestinal bleeding did not occur in the other nine patients. Overall mortality was 27%, mortality attributable to upper gastrointestinal bleeding was 0%. Pneumonia developed in one patient after initiating omeprazole therapy and was present upon the initiation of omeprazole therapy in another patient. The mean length of prophylaxis was five days.

A pharmacoeconomic analysis revealed a difference in the total cost of care for the prophylaxis of SRMD:

ranitidine (Zantac®) continuous infusion intravenously (150 mg/24 hours) x five days $125.50;

cimetidine (Tagamet®) continuous infusion intravenously (900 mg/24 hours) x five days $109.61;

sucralfate one gm slurry four times a day per (ng) tube x five days $73.00; and

SOS regimen per (ng) tube x five days $65.70.

Conclusion:

This example illustrates the efficacy of the simplified omeprazole solution of the present invention based on the increase in gastric pH, safety and cost/convenience of the omeprazole solution/suspension as a method for SRMD prophylaxis.

Example II

Experiments were carried out in order to determine the effect of the omeprazole solution/suspension (omeprazole/sodium bicarbonate solution) administration on the accuracy on subsequent pH measurements through a nasogastric tube.

Methods:

The omeprazole solution/suspension was prepared by mixing 10 ml of 8.4% sodium bicarbonate with the contents of a 20 mg capsule of omeprazole (Merck & Co. Inc., West Point, PA) to yield a solution/suspension having a final omeprazole concentration of 2 mg/ml. After mixing the

omeprazole solution/suspension, it was administered into the stomach, usually, through a nasogastric (ng) tube. Nasogastric tubes from nine different institutions were gathered for an evaluation 400 mg omeprazole solution/suspension was prepared as described above. Artificial gastric fluid (gf) was prepared according to the USP. pH recordings were made in triplicate using a Microcomputer Portable pH meter model 6007 (Jenco Electronics Ltd., Taipei, Taiwan). [1] First the terminal portion (tp) of the nasogastric tubes was placed into a glass beaker containing the gastric fluid. A 5 ml aliquot of gastric fluid was aspirated through each tube and the pH recorded, this was called the "pre-omeprazole solution/suspension measurement". [2] Secondly, the terminal portion (tp) of each of the nasogastric tubes was removed from the beaker of gastric fluid and placed into an empty beaker. Twenty (20) mg of omeprazole solution/suspension was delivered through each of the nasogastric tubes and flushed with 10 ml of tap water. The terminal portion (tp) of each of the nasogastric tubes was placed back into the gastric fluid. After a one hour incubation, a 5 ml aliquot of gastric fluid was aspirated through each nasogastric tube and the pH recorded, this was called the "after 1st dose SOS measurement". [3] After an additional hour had passed, the second step was repeated, this was called the "after 2nd ND dose SOS measurement". In addition to the pre-SOS measurement, the pH of the gastric fluid was checked in triplicate after steps [2] and [3]. A change in the pH measurements of +/- 0.3 units was

considered significant. The Friedman test was used to compare the results. The Friedman test is a two way analysis of variance which is used when more than two related samples are of interest, as in repeated measurements.

Results:

The results of this experiments are outlined in Table 1. Table 1 illustrates the results of the pH measurements that were taken during the course of the experiment. These results illustrate that there were no statistically significantly latent effects of omeprazole solution/suspension administration (per nasogastric tube) on the accuracy of subsequent pH measurements obtained through the same nasogastric tube.

Example III

Experiments were performed in order to determine the efficacy, safety, and cost of simplified omeprazole suspension in mechanically ventilated critically ill patients who have at least one additional risk factor for stress-related mucosal damage.

Methods:

Patients: Seventy-five adult, mechanically ventilated patients with at least one additional risk factor for stress-related mucosal damage.

Interventions: Patients received 20 ml omeprazole suspension (containing 40 mg of omeprazole) initially,

followed by a second 20 ml dose six-eight hours later, then 10 ml (20 mg) daily. Omeprazole solution/suspension according to the present invention was administered through a nasogastric tube, followed by 5-10 ml of tap water. The nasogastric tube was clamped for one-two hours after each administration.

Measurements and Main Results: The primary outcome measure was clinically significant gastrointestinal bleeding determined by endoscopic evaluation, nasogastric aspirate examination, or heme-positive coffee ground material that did not clear with lavage and was associated with a five percent decrease in hematocrit. Secondary efficacy measures were gastric pH measured four hours after omeprazole was first administered, mean gastric pH after omeprazole was started, and the lowest gastric pH during omeprazole therapy. Safety-related outcomes included the incidence of adverse events and the incidence of pneumonia. No patient experienced clinically significant upper gastrointestinal bleeding after receiving omeprazole suspension. The four-hour post omeprazole gastric pH was 7.1 (mean), the mean gastric pH after starting omeprazole was 6.8 (mean) and the lowest pH after starting omeprazole was 5.6 (mean). The incidence of pneumonia was twelve percent. No patient in this high-risk population experienced an adverse event or a drug interaction that was attributable to omeprazole.

Conclusions: Omeprazole suspension prevented clinically significant upper gastrointestinal bleeding and

maintained gastric pH above 5.5 in mechanically ventilated critical care patients without producing toxicity.

Materials and Methods:

The study protocol was approved by the Institutional Review Board for the University of Missouri at Columbia.

Study Population: All adult (>18 years old) patients admitted to the surgical intensive care and burn unit at the University of Missouri Hospital with an intact stomach, a nasogastric tube in place, and an anticipated intensive care unit stay of at least forty-eight hours were considered for inclusion in the study. To be included patients also had to have a gastric pH of <4, had to be mechanically ventilated and have one of the following additional risk factors for a minimum of twenty-four hours after initiation of omeprazole suspension: head injury with altered level of consciousness, extensive burns (>20% Body Surface Area), acute renal failure, acid-base disorder, multiple trauma, coagulopathy, multiple operative procedures, coma, hypotension for longer than one hour or sepsis (see Table 2). Sepsis was defined as the presence of invasive pathogenic organisms or their toxins in blood or tissues resulting in a systematic response that included two or more of the following: temperature greater than 38°C or less than 36°C, heat rate greater than 90 beats/minute, respiratory rate greater than 20 breaths/minute (or $_pO_2$ less than 75 mm Hg), and white blood cell count greater than 12,000 or less than 4000 cells/mm^3 or more than 10 percent bands (Bone, 1991). Patients in whom H_2-antagonist

therapy had failed or who experienced an adverse event while receiving H_2-antagonist therapy were also included.

Patients were excluded from the study if they were receiving azole antifungal agents through the nasogastric tube; were likely to swallow blood (e.g., facial and/or sinus fractures, oral lacerations); had severe thrombocytopenia (platelet count less than 30,000 cells/mm^3); were receiving enteral feedings through the nasogastric tube; or had a history of vagotomy, pyloroplasty, or gastroplasty. In addition, patients with a gastric pH above four for forty-eight hours after ICU admission (without prophylaxis) were not eligible for participation. Patients who developed bleeding within the digestive tract that was not stress-related mucosal damage (e.g., endoscopically verified variceal bleeding or Mallory-Weiss tears, oral lesions, nasal tears due to placement of the nasogastric tube) were excluded from the efficacy evaluation and categorized as having non-stress-related mucosal bleeding. The reason for this exclusion is the confounding effect of non-stress-related mucosal bleeding on efficacy-related outcomes, such as the use of nasogastric aspirate inspection to define clinically significant upper gastrointestinal bleeding.

Study Drug Administration: Omeprazole solution/suspension was prepared immediately before administration by the patient's nurse using the following instructions: 1) Empty the contents of one or two 20 mg omeprazole capsule(s) into an empty 10 ml syringe (with 20

gauge needle in place) from which the plunger has been removed. (Omeprazole delayed-release capsules, Merck & Co., Inc., West Point, PA). 2) Replace the plunger and uncap the needle. 3) Withdraw 10 ml of 8.4% sodium bicarbonate solution or 20 ml if 40 mg given (Abbott Laboratories, North Chicago, IL). The resultant preparation should contain 2 mg omeprazole per ml of 8.4% sodium bicarbonate. 4) Allow the enteric coated pellets of omeprazole to completely breakdown, 30 minutes (agitation is helpful). The omeprazole in the resultant preparation is partially dissolved and partially suspended. The preparation should have a milky white appearance with fine sediment and should be shaken before using. The solution/suspension was not administered with acidic substances. A high pressure liquid chromatography study was performed that has demonstrated that this preparation of simplified omeprazole suspension maintains >90% potency for seven days at room temperature. This preparation remained free of bacterial and fungal contamination for thirty days when stored at room temperature (see Table 5).

The initial dose of omeprazole solution/suspension was 40 mg, followed by a second 40 mg dose 6-8 hours later, then a 20 mg daily dose administered at 8:00 AM. Each dose was administered through the nasogastric tube. The nasogastric tube was then flushed with 5-10 ml of tap water and clamped for at least one hour. Omeprazole therapy was continued until there was no longer a need for stress ulcer prophylaxis (usually after the nasogastric tube removed and

the patient was taking water/food by mouth, or after the patient was removed from mechanical ventilation).

Primary Outcome Measures: The primary outcome measure in this study was the rate of clinically significant stress-related mucosal bleeding defined as endoscopic evidence of stress-related mucosal bleeding or bright red blood per nasogastric tube that did not clear after a 5-minute lavage or persistent Gastroccult (SmithKline Diagnostics, Sunnyville, CA) positive coffee ground material for four consecutive hours that did not clear with lavage (at least 100 ml) and produced a 5% decrease in hematocrit.

Secondary Outcome Measures: The secondary efficacy measures were gastric pH measured four hours after omeprazole was administered, mean gastric pH after starting omeprazole and lowest gastric pH during omeprazole administration. Gastric pH was measured immediately after aspirating gastric contents through the nasogastric tube. pH paper (pHydrion improved pH papers, Microessential Laboratory, Brooklyn, NY) was used to measure gastric aspirate pH. The pH range of the test strips was 1 to 11, in increments of one pH unit. Gastric pH was measured before the initiation of omeprazole solution/suspension therapy, immediately before each dose, and every four hours between doses.

Other secondary outcome measures were incidence of adverse events (including drug interactions) and pneumonia.

Any adverse event that developed during the study was recorded. Pneumonia was defined using indicators adapted from the Centers for Disease Prevention and Control definition of nosocomial pneumonia (Garner et al., 1988). According to these criteria, a patient who has pneumonia is one who has rales or dullness to percussion on physical examination of the chest or has a chest radiograph that shows new or progressive infiltrate(s), consolidation, cavitation, or pleural effusion and has at least two of the following present: new purulent sputum or changes in character of the sputum, an organism isolated from blood culture, fever or leukocytosis, or evidence of infection from a protective specimen brush or bronchoalveolar lavage. Patients who met the criteria for pneumonia and were receiving antimicrobial agents for the treatment of pneumonia were included in the pneumonia incidence figure. These criteria were also used as an initial screen before the first dose of study drug was administered to determine if pneumonia was present prior to the start of omeprazole suspension.

Cost of Care Analysis: A pharmacoeconomic evaluation of stress ulcer prophylaxis using omeprazole solution/suspension was performed. The evaluation included total drug cost (acquisition and administration), actual costs associated with adverse events (e.g., psychiatry consultation for mental confusion), costs associated with clinically significant upper gastrointestinal bleeding. Total drug cost was calculated by adding the average

institutional costs of omeprazole 20 mg capsules, 50 ml sodium bicarbonate vials, and 10 ml syringes with needle; nursing time (drug administration, pH monitoring); pharmacy time (drug preparation); and disposal costs. Costs associated with clinically significant upper gastrointestinal bleeding included endoscopy charges and accompanying consultation fees, procedures required to stop the bleeding (e.g., surgery, hemostatic agents, endoscopic procedures), increased hospital length of stay (as assessed by the attending physician), and cost of drugs used to treat the gastrointestinal bleeding.

Statistical Analysis: The paired t-test (two-tailed) was used to compare gastric pH before and after omeprazole solution/suspension administration and to compare gastric pH before omeprazole solution/suspension administration with the mean and lowest gastric pH value measured after beginning omeprazole.

Results:

Seventy-seven patients met the inclusion and exclusion criteria and received omeprazole solution/suspension (see Figure 2). Two patients were excluded from the efficacy evaluation because the protocol for omeprazole administration was not followed. In one case, the omeprazole enteric-coated pellets had not completely broken down prior to the administration of the first two doses, which produced an erratic effect on gastric pH. The gastric pH increased to above six as soon as the patient was given a dose of omeprazole solution/suspension (in

which the enteric coated pellets of omeprazole had been allowed to completely breakdown).

The reason for the second exclusion was that nasogastric suctioning was not turned off after the omeprazole dose was administered. This resulted in a transient effect on gastric pH. The suction was turned off with subsequent omeprazole doses, and control of gastric pH was achieved. Two patients were considered efficacy failures because omeprazole failed to maintain adequate gastric pH control on the standard omeprazole 20 mg/day maintenance dose. When the omeprazole dose was increased to 40 mg/day (40 mg once/day or 20 mg twice/day), gastric pH was maintained above four in both patients. These two patients were included in the safety and efficacy evaluations, including the gastric pH analysis. After the two patients were declared failures, their pH values were no longer followed.

The ages of the remaining seventy-five patients ranged from eighteen to eighty-seven years; forty-two patients were male and thirty-three were female. All patients were mechanically ventilated during the study. Table 2 shows the frequency of risk factors for stress-related bleeding that were exhibited by the patients in this study. The most common risk factors in this population were mechanical ventilation and major surgery. The range of risk factors for any given patient was two to ten, with a mean of 3 (±1) (standard deviation). Five patients enrolled in the study had developed clinically significant bleeding while

receiving continuous infusions of ranitidine (150 mg/24 hr) or cimetidine (900 mg/24 hr). In all five cases, the bleeding subsided and the gastric pH rose to above five within thirty-six hours after initiating omeprazole therapy. Three patients were enrolled after having developed two consecutive gastric pH values below three while receiving an H_2-antagonist (in the doses outlined above). In all three cases, gastric pH rose to above five within four hours after omeprazole therapy was initiated. Four other patients were enrolled in this study after experiencing confusion (n=2) or thrombocytopenia (n=2) during H_2-antigens therapy. Within thirty-six hours of switching therapy, these adverse events resolved.

Stress-related Mucosal Bleeding and Mortality: None of the sixty-five patients who received simplified omeprazole suspension as their initial prophylaxis against stress-related mucosal bleeding developed overt or clinically significant upper gastrointestinal bleeding. In four of the five patients who had developed upper gastrointestinal bleeding before study entry, bleeding diminished to the presence of occult blood only (Gastroccult-positive) within eighteen hours of starting omeprazole suspension; bleeding stopped in all patients within thirty-six hours. The overall mortality rate in this group of critically ill patients was eleven percent. No death was attributable to upper gastrointestinal bleeding or the use of omeprazole solution/suspension.

Gastric pH: The mean (± standard deviation) pre-omeprazole gastric pH was 3.5 ± 1.9. Within four hours of omeprazole administration, the gastric pH rose to 7.1 ± 1.1 (se Figure 3); this difference was significant ($p<0.001$). The differences between pre-omeprazole gastric pH and the mean and lowest gastric pH measurements during omeprazole administration (6.8 ± 0.6 and 5.6 ± 1.3, respectively) were also statistically significant ($p<0.001$).

Safety: Omeprazole solution/suspension was well tolerated in this group of critically ill patients. Only one patient with sepsis experienced an adverse event that may have been drug-related thrombocytopenia. However, the platelet count continued to fall after omeprazole was stopped. The platelet count then returned to normal despite reinstitution of omeprazole therapy. Of note, one patient on a jet ventilator continuously expelled all liquids placed in her stomach up and out through her mouth, and thus was unable to continue on omeprazole. No clinically significant drug interactions with omeprazole were noted during the study period. As stated above, metabolic alkalosis is a potential concern in patients receiving sodium bicarbonate. However, the amount of sodium bicarbonate in omeprazole solution/suspension was small (12 mEq/10 ml) and no electrolyte abnormalities were found.

Pneumonia: Pneumonia developed in nine (12%) patients receiving omeprazole solution/suspension. Pneumonia was

present in an additional five patients before the start of omeprazole therapy.

Pharmacoeconomic evaluation: The average length of treatment was nine days. The cost of care data are listed in Tables 3 and 4. The costs of drug acquisition, preparation, and delivery for some of the traditional agents used in the prophylaxis of stress-related upper gastrointestinal bleeding are listed in Table 3. There were no costs to add from toxicity associated with omeprazole solution/suspension. Since two of seventy-five patients required 40 mg of omeprazole solution/suspension daily to adequately control gastric pH, the acquisition/preparation cost should reflect this. The additional 20 mg of omeprazole with vehicle adds seven cents per day to the cost of care. Therefore, the daily cost of care for omeprazole solution/suspension in the prophylaxis of stress-related mucosal bleeding was $12.60 see Table 4.

Omeprazole solution/suspension is a safe and effective therapy for the prevention of clinically significant stress-related mucosal bleeding in critical care patients. The contribution of many risk factors to stress-related mucosal damage has been challenged recently (6). All of the patients in this study had at least one risk factor that has clearly been associated with stress-related mucosal damage - mechanical ventilation. Previous trials and data from a recently published study show that stress ulcer prophylaxis is of proven benefit in patients at risk

and, therefore, it was thought to be unethical to include a placebo group in this study. No clinically significant upper gastrointestinal bleeding occurred during omeprazole solution/suspension therapy. Gastric pH was maintained above 4 on omeprazole 20 mg/day in seventy-three of seventy-five patients. No adverse events or drug interaction associated with omeprazole were encountered.

Example IV

The anti-microbial or bacteriostatic effects of the omeprazole solution/suspension were analyzed by applicants.

An omeprazole solution/suspension made according to the present invention was stored at room temperature for four weeks and then was analyzed for fungal and bacterial growth.

Results:

Following four weeks of storage at room temperature, no bacterial or fungal growth was detected.

An omeprazole solution/suspension made in accordance with the present invention was stored at room temperature for twelve weeks and then was analyzed for fungal and bacterial growth.

Results:

After twelve weeks of incubation at room temperature, no fungal or bacterial growth was detected.

The results of these experiments illustrate the stability and bacteriostatic characteristics of the omeprazole solution/suspension of the present invention.

Throughout this application various publications and patents are referenced by citation and number. Full citations for the publication are listed below. The disclosure of these publications and patents in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

The invention has been described in an illustrative manner, and it is to be understood the terminology used is intended to be in the nature of description rather than of limitation.

Obviously, many modifications and variations of the present invention are possible in light of the above teachings. Therefore, it is to be understood that within the scope of the appended claims, reference numerals are merely for convenience and are not to be in any way limiting, the invention may be practiced otherwise than as specifically described.

TABLE 1

	ng1	ng2	ng3	ng4	ng5	ng6	ng7	ng8	ng9
[1] gf Pre SOS	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
[2] gf β 1st dose	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
1.3 ← check of gf pH									
[3] gf β 2nd dose	1.3	1.3	1.4	1.4	1.4	1.3	1.4	1.3	1.3
1.3 ← check of gf pH									

SOS pH = 5.0

TABLE 2

Mech Vent	Major Surgery	Multi - trauma	Head Injury	Hypo-tension	Renal Failure	Sepsis	Multiple Operation	Acid / Base	Coma	Liver Failure	Burn
75	61	35	16	14	14	14	12	10	4	2	2

Risk factors present in patients in this study (n=75)

TABLE 3

RANITIDINE (day 1 -9)		
Ranitidine	150mg/24 hr	Per day 6.15
Ancillary Product (1)	Piggyback (60%)	0.75
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	.40
Sterile Prep required	yes	
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	8.00
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs x 50%	14.50
TOTAL for 9 days ---------->		304.20
Note: Does not include the cost of failure and/or adverse effect.		
RANITIDINE Cost per day ---------->		*33.80*
CIMETIDINE (day 1 - 9)		
Cimetidine	900 mg/24 hr	Per day 3.96
Ancillary Product (1)	Piggyback	1.25
Ancillary Product (2)	micro tubing (etc.)	2.00
Ancillary Product (3)	filter	.40
Sterile Prep required	yes	
R.N. time ($24/hr)	20 minutes/day (includes pH monitoring)	8.00
R.Ph. time, hood maint.	3 minutes ($40/hr)	2.00
Pump cost	$29/24 hrs x 50%	14.50
TOTAL for 9 days ---------->		288.99
Note: Does not include the cost of failure and/or adverse effect.		
CIMETIDINE Cost per day ---------->		*32.11*
SUCRALFATE (day 1 - 9)		
Sucralfate	1 Gm x 4	Per day 2.40
Ancillary Product (1)	syringe	.20
Sterile Prep required	no	
R.N. time ($24/hr)	30 minutes/day (includes pH monitoring)	12.00
TOTAL for 9 days ---------->		131.40
Note: Does not include the cost of failure and/or adverse effect.		
SUCRALFATE Cost per day ---------->		*14.60*

Acquisition, preparation and delivery costs of traditional agents.

TABLE 4

The average length of treatment was 9 days. Cost of care was calculated from these data:

		Per day	Total
OMEPRAZOLE (day 1)			
Product acquisition cost	40 mg load x 2 (5.66/dose)	11.32	11.32
Ancillary product	materials for solution preparation	0.41	0.41
Ancillary product	syringe w/needle	0.20	0.40
Sterile preparation required	no		
SOS preparation time (R.N.)	6 minutes	2.40	4.80
R.N. time ($24/hr)	21 minutes/day (includes pH monitoring)	8.40	8.40
OMEPRAZOLE (days 2 - 9)			
Product acquisition cost	20 mg per day	2.83	22.65
Ancillary product	materials for solution preparation	0.41	0.82
Ancillary product	syringe w/needle	0.20	1.60
Sterile preparation required	no		
SOS preparation time (R.N.)	6 minutes	2.40	4.80
R.N. time ($24/hr)	18 minutes/day (includes pH monitoring)	8.00	57.60
2/75 patient require 40 mg simplified omeprazole solution per day (days 2-9)			0.63
No additional cost for adverse effects or for failure			
TOTAL ---------->			113.43
Simplified Omeprazole Solution Cost per day ---------->			*12.60*

Pharmacoeconomic evaluation of omeprazole cost of care

TABLE 5

Time	Control	1 hour	24 hour	2 day	7 day	14 day
Conc (mg/ml)	2.01	2.07	1.94	1.96	1.97	1.98

Stability of Simplified Omeprazole Solution at room temperature (25°C)
Values are the mean of three samples

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CLAIMS

1. A liquid oral pharmaceutical composition, comprising:

a) a proton pump inhibitor; and

b) at least one bicarbonate salt of a Group IA metal; wherein if said inhibitor is omeprazole, it must be present in a concentration greater than 1.2 mg/ml, and if said inhibitor is lansoprazole, it must be present in a concentration greater than 0.3 mg/ml.

2. The liquid oral pharmaceutical composition as recited in Claim 1 further comprising a parietal cell activator.

3. The liquid oral pharmaceutical composition as recited in Claim 2 wherein said activator is selected from the group consisting of chocolate, sodium bicarbonate, and calcium and salts, and mixtures thereof.

4. The liquid oral pharmaceutical composition as recited in Claim 1 further comprising a flavoring agent.

5. A solid oral pharmaceutical composition, comprising:

a) A proton pump inhibitor; and

b) At least one bicarbonate salt of a Group IA metal; wherein said composition is in a dosage form selected from the group

consisting of a powder, a tablet, a capsule, an effervescent powder, an effervescent tablet, pellets and granules, and wherein said dosage form is not enteric coated or time-released.

6. The solid oral pharmaceutical composition, as recited in Claim 5 further comprising a parietal cell activator.

7. A method of treating gastric acid disorders comprising administering to a patient an oral pharmaceutical composition comprising a proton pump inhibitor and at least one bicarbonate salt of a Group IA metal wherein said administering step comprises providing a patient with a single dose of the pharmaceutical composition without requiring further administration of the at least one buffering agent.

8. An oral pharmaceutical to be administered in combination with a proton pump inhibitor comprising at least one bicarbonate salt of a Group IA metal wherein said composition is in a dosage form selected from the group consisting of a powder, a tablet, a capsule, an effervescent powder, an effervescent tablet, pellets and granules, and wherein said dosage form is not enteric coated or time-released.

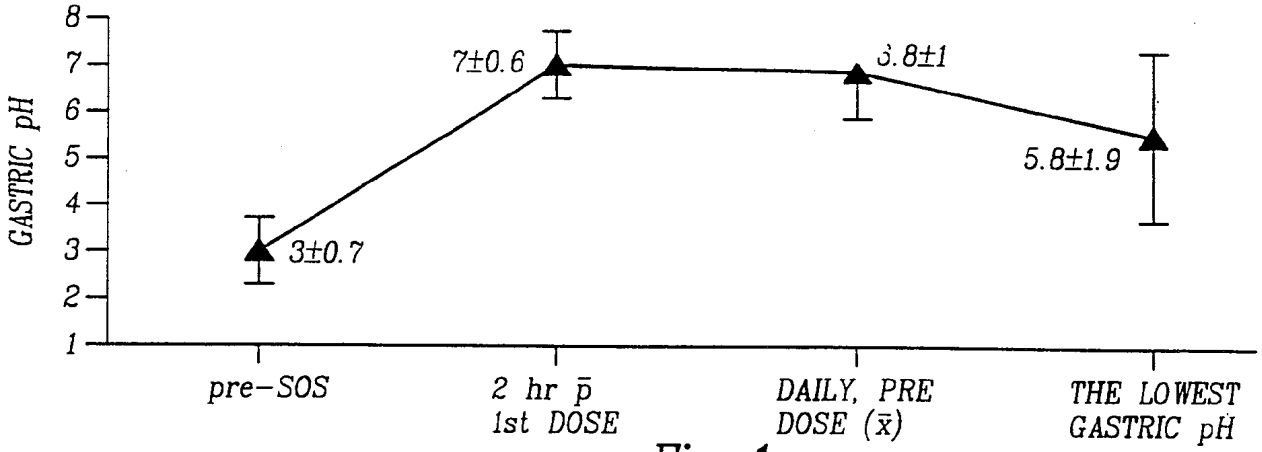
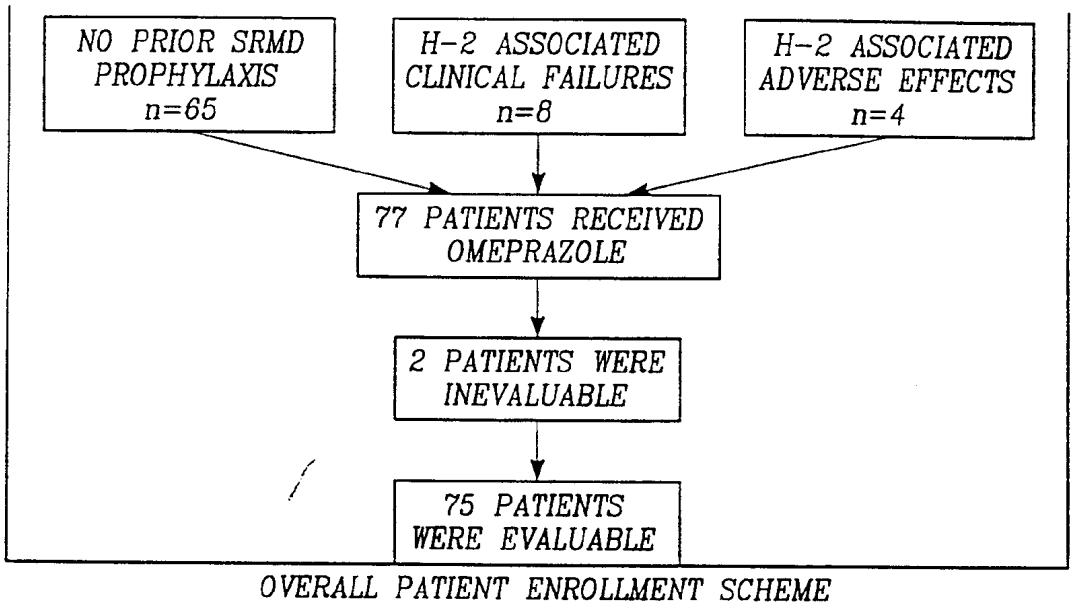


Fig-1



OVERALL PATIENT ENROLLMENT SCHEME

Fig-2

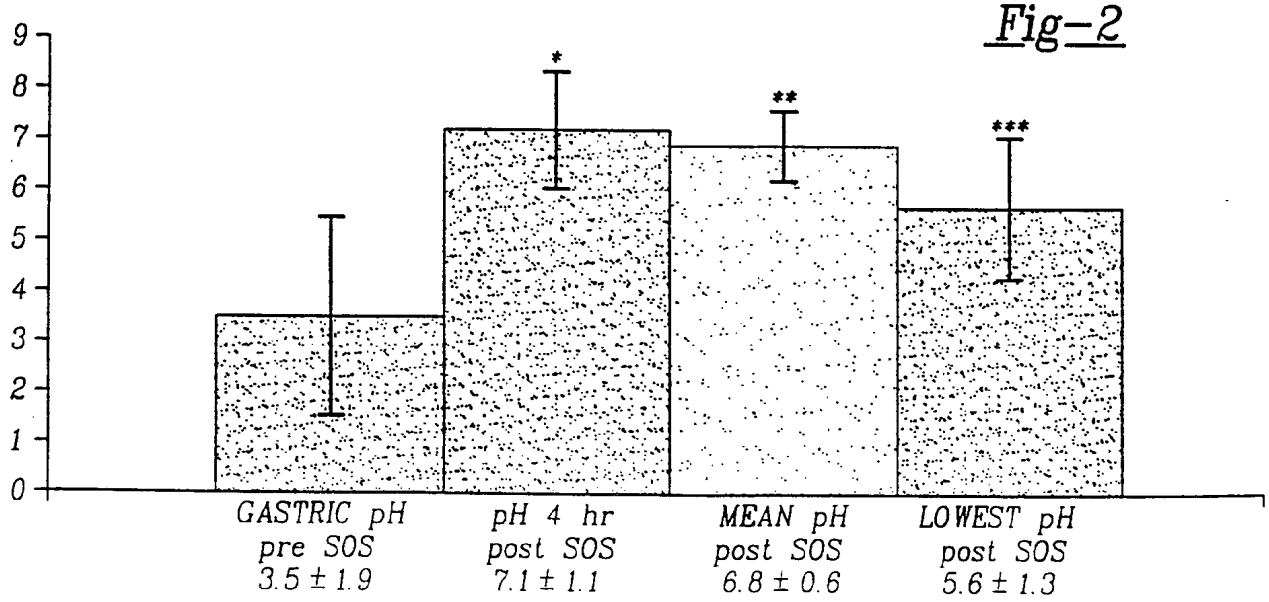
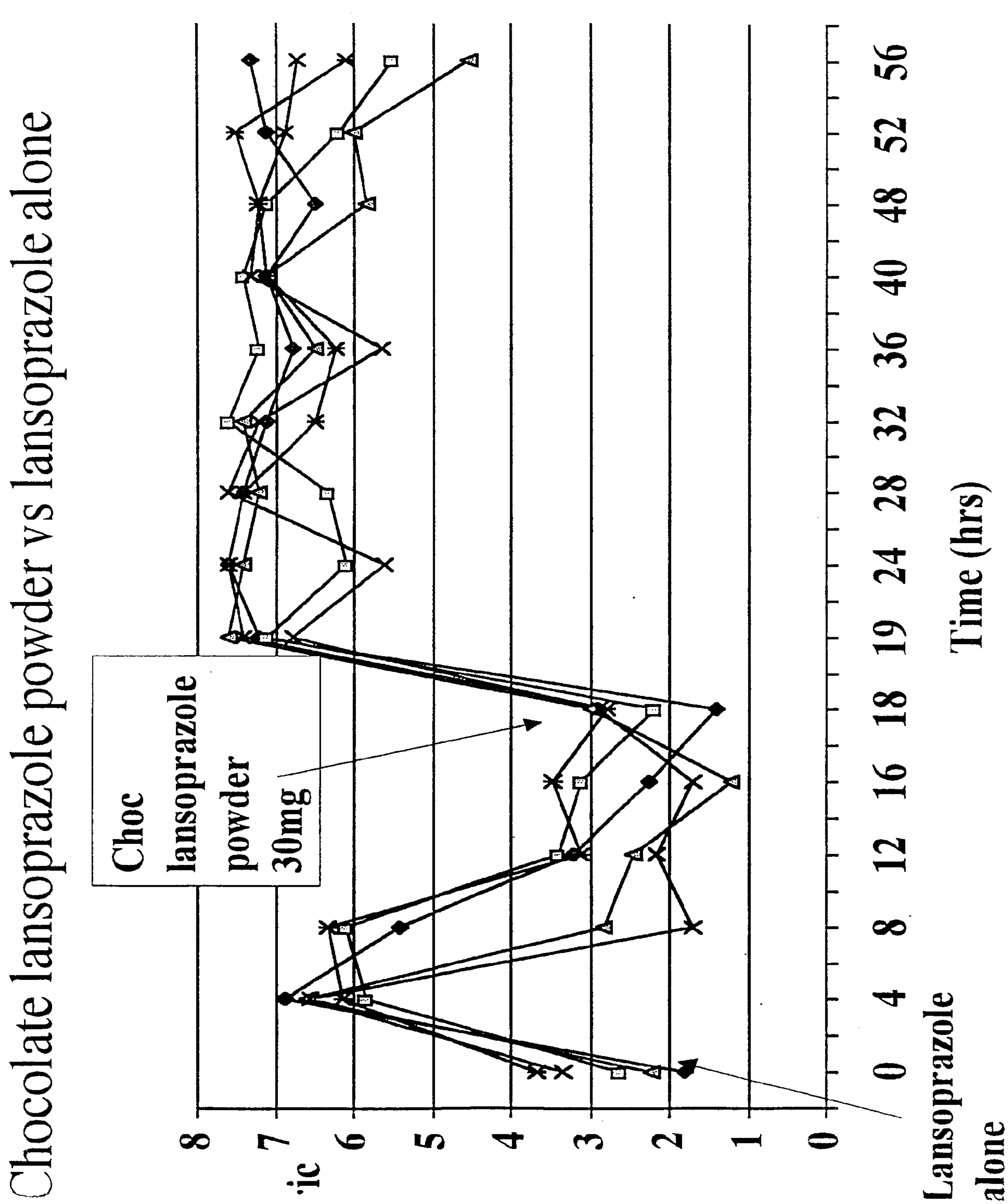


Fig-3

FIGURE 4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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 9/24, 31/44, 47/38

A1

(11) International Publication Number: **WO 00/27366**

(43) International Publication Date: 18 May 2000 (18.05.00)

(21) International Application Number: PCT/SE99/01989

(22) International Filing Date: 3 November 1999 (03.11.99)

(30) Priority Data:
9803772-4 5 November 1998 (05.11.98) SE

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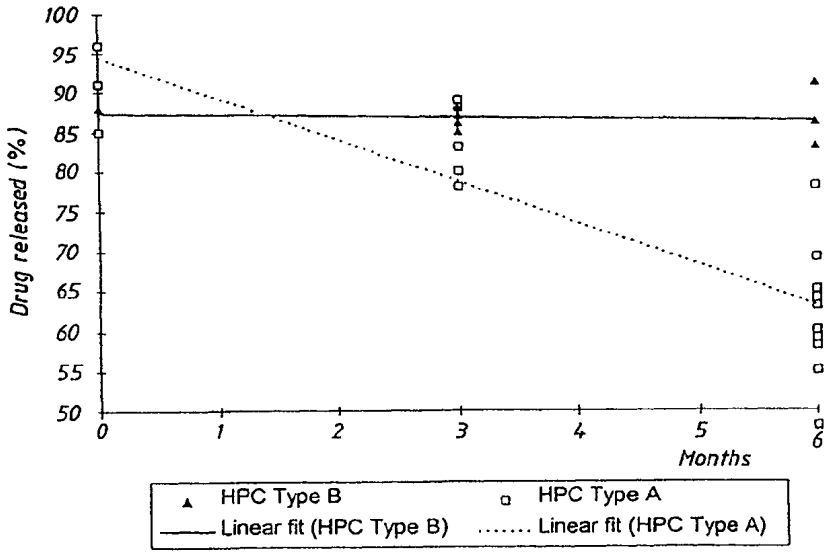
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL FORMULATION COMPRISING OMEPRAZOLE



(57) Abstract

An enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, one of the single enantiomers of omeprazole and an alkaline salt of one of the single enantiomers of omeprazole, wherein the formulation comprises a core material that comprises the active ingredient and optionally an alkaline reacting compound, the active ingredient is in admixture with a pharmaceutically acceptable excipient, such as for instance a binding agent, and on said core material a separating layer and an enteric coating layer. A hydroxypropyl cellulose (HPC) with a specific cloud point is used in the manufacture of the claimed pharmaceutical formulations. Furthermore, the application describes the processes for their preparation and the use of the claimed formulations in medicine.

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PHARMACEUTICAL FORMULATION COMPRISING OMEPRAZOLE

Field of the invention.

The present invention relates to an oral pharmaceutical formulation comprising the acid labile H^+, K^+-ATPase inhibitor omeprazole, an alkaline salt of omeprazole, one of the single enantiomers thereof or an alkaline salt of one of the single enantiomers of omeprazole. In the following these compounds are referred to as omeprazole. The formulation is in the form of a multiple unit dosage form that comprises enteric coating layered units of omeprazole. More specifically, the units comprise a core material that comprises omeprazole optionally in admixture with an alkaline reacting substance, and in admixture with one or more pharmaceutically acceptable excipients such as a binding agent, a filling agent and/or a disintegrating agent. Furthermore, each unit comprises a separating layer to separate the enteric coating layer from the core material. The separating layer comprises a specific quality of hydroxypropyl cellulose (HPC), and optionally pharmaceutical excipients. More specifically, the HPC quality is defined by having a specific cloud point.

Furthermore, the present invention refers to the use of the specific quality of HPC in the manufacture of a pharmaceutical formulation comprising omeprazole, and the use of such a pharmaceutical formulation in medicine.

Background of the invention.

Omeprazole, an alkaline salt thereof, the single enantiomers of omeprazole and an alkaline salt of the single enantiomers of omeprazole, all compounds hereinafter referred to as omeprazole, are used in the treatment of gastric acid related diseases. Omeprazole and pharmaceutically acceptable salts thereof are described in EP 5129, and some specific alkaline salts of omeprazole are described in EP 124 495 and WO95/01977. Certain salts of the single enantiomers of omeprazole and their preparations are described in WO94/27988.

Omeprazole is generally known to be useful for inhibiting gastric acid secretion in mammals and man by controlling gastric acid secretion at the final step of the acid secretory pathway. Thus, in a more general sense, it may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcers and duodenal ulcers. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with non ulcer dyspepsia, in patients with symptomatic gastro-oesophageal reflux disease, and in patients with gastrinomas. It may also be used in a patient in intensive care situations, in a patient with acute upper gastrointestinal bleeding, pre-and post-operatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, it may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these, as well as in the treatment or prophylaxis of inflammatory conditions in mammals, including man.

Omeprazole is, however, susceptible to degradation or transformation in acidic and neutral media. The degradation is catalyzed by acidic compounds and is stabilized in mixtures with alkaline compounds. The chemical stability of omeprazole is also affected by moisture, heat, and organic solvents and to some degree by light.

Due to the chemical stability properties of omeprazole, it is obvious that an oral solid dosage form comprising omeprazole must be protected from contact with the acidic gastric juice. Omeprazole must also be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

A pharmaceutical oral dosage form of omeprazole is best protected from contact with acidic gastric juice by an enteric coating layer. For instance, EP 247 983 describes enteric coated formulations of omeprazole. Such as formulation contains omeprazole in the form of a core unit containing omeprazole together with an alkaline salt or containing an alkaline salt of omeprazole optionally together with an alkaline salt, the core unit is layered with a

separating layer and an enteric coating layer. In WO 96/01623 a multiple unit tableted dosage formulation comprising omeprazole is described.

The oral formulations described in EP 247 983 and the tablet formulations described in WO 96/01623 are examples of enteric coating layered formulations that comprise or optionally comprise a separating layer to separate the acidic enteric coating material from omeprazole being an acid susceptible substance. HPC may be used in a layer that separates the core material from the enteric coating layer in the described formulations. All ingredients, including HPC qualities, used in a pharmaceutical preparation must fulfil strict criteria, such as for instance requirements defined in pharmacopoeial monographs.

The rate of release of omeprazole from a pharmaceutical dosage form can influence the total extent of absorption of omeprazole into the general circulation (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). Therefore the limits for rate of release of the omeprazole from the pharmaceutical formulation are stated in the marketing approval for the products. The release of omeprazole is affected both by the chemical stability of the active substance and the release stability of the pharmaceutical formulation. If the formulation is unstable with respect to the release rate, the drug will have a non-accepted storage time, i.e. the expiration period for the product will be too short.

It has now surprisingly been found that different batches of HPC, which fulfil all pharmacopoeial requirements, used as material for the separating layer in a pharmaceutical formulation comprising omeprazole, may result in different release rate over time. Thus, the storage period for the pharmaceutical formulation may not be acceptable. One parameter of interest for the HPC's influence on the release stability is its water solubility.

The aqueous solubility of HPC decreases with increasing temperature due to polymer phase separation. This is observed as a clouding of the polymer solution when the temperature is increased. Cloud point is the temperature at which this polymer phase

separation occurs. Cloud point is determined by measuring the light transmission through the polymer solution. The light transmission of a specific system where the polymer is dissolved, that is a transparent polymer solution without clouding, is defined as light transmission 100 %. In this patent application cloud point is defined as the temperature where the light transmission of a specific system is 96% when a commercial instrument from Mettler is used. For other cloud point systems and instruments another light transmisson may be specified for each system.

One problem that can be avoided by the new formulation and use of a specific quality of HPC, is that the storage period for the dosage form can be extended and guarantied. From an economical aspect it is advantageous to specify and check the HPC quality thereby keeping a long expire date of the dosage form.

Outline of the invention.

It has now been found that a quality of HPC with a cloud point of not less than 38°C determined as the temperature where the light transmission of a specified system is 96% measured by a Mettler FP90/FP 81C instrument is desirable in an enteric coating layered pharmaceutical formulation comprising omeprazole. Preferably, the HPC should have a cloud point of not less than 40°C, and more preferably not less than 41°C. When another instrument is used for determination, the cloud point may be specified in other terms. An upper limit for the cloud point is not critical and therefore there is no need to specify that.

The HPC is used as a constituent of a separating layer separating the core material comprising omeprazole from the enteric coating layer. The HPC quality defined in the present patent application is desirable in fulfilling the criteria on release rate stability and to be suitable for oral administration forms comprising omeprazole.

Detailed description of the drawings.

Figure 1 shows two graphs representing two different dosage forms based on two qualities of HPC named Type A and Type B. The graphs show released omeprazole from the dosage forms after 3 months and 6 months storage at accelerated conditions at 40°C and 75% relative humidity. The two HPC qualities are used as a constituent of the separating layer described in Example 2 below. With a separating layer comprising HPC Type A the release rate of omeprazole over time has decreased. With the HPC Type B the release rate of omeprazole over time is almost the same as for a freshly produced product.

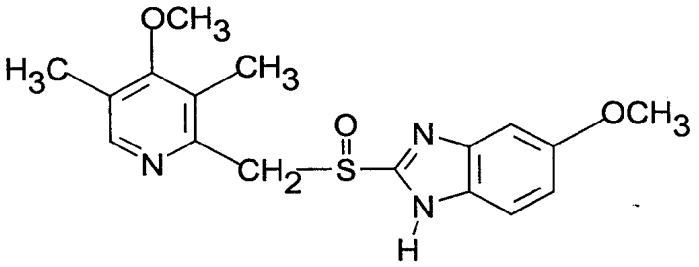
Figure 2 shows two graphs representing two different qualities of HPC named Type A and Type B. The graphs show cloud point determinations for the two HPC qualities used as a constituent of the separating layer described in Examples 1 - 3 below.

Figure 3a) and Figure 3b) show graphs representing two different dosage forms based on two qualities of HPC named Type A and Type B. Figure 3a) shows released omeprazole from dosage forms comprising HPC type A, i.e. a reference. Figure 3b) shows released omeprazole from dosage forms comprising HPC type B, i.e. according to the invention. The two HPC qualities are used as a constituent of the separating layer described in Example 1 below.

Detailed description of the invention.

Core materials.

Omeprazole with formula Ia, is preferably formulated into an oral composition in the form of a pharmaceutically acceptable salt, such as an alkaline salt selected from the group of the Mg^{2+}, Ca^{2+}, Na^{+} and K^{+} salts, more preferably the Mg^{2+} salt. Omeprazole may also be used in the form of one of the single enantiomers of omeprazole or an alkaline salt of one of the single enantiomers of omeprazole, especially an alkaline salt of the (-)-enantiomer of omeprazole, and more preferably the Mg^{2+} salt of the (-)-enantiomer of omeprazole.



(Ia)

The core material for the individually enteric coating layered pellets can be composed and formulated according to different principles, such as described in EP 247 983 and WO 96/01623 hereby incorporated by reference. For instance, omeprazole is mixed with one or more pharmaceutical constituents to obtain preferred handling and processing properties and also to obtain a suitable concentration of omeprazole in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used.

Preferably, omeprazole, optionally after mixing with an alkaline compound, is mixed with suitable constituents including a binding agent and formulated into a core material. Said core materials may be produced by extrusion/spheronization, balling or compression and by utilizing different process equipment. The formulated core materials may have a size of less than approximately 2 mm. The manufactured core materials can be layered further with additional ingredients, optionally comprising active substance, and/or be used for further processing.

Alternatively, inert seeds layered with active substance (the active substance is optionally mixed with alkaline compounds) can be used as the core material for the further processing. The seeds, which are to be layered with the active substance, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures.

Before the seeds are layered, for instance by using granulating or spray coating/layering equipment, omeprazole is mixed with a binding agent and optionally further components. Such further components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures.

The binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, microcrystalline cellulose and carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants, such as for instance sodium lauryl sulphate.

The active substance may also be mixed with an alkaline pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate co-precipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $Mg_6Al_2(OH)_{16}CO_3.4H_2O$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxy methyl amino methane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

Separating layer(s)

The core material containing omeprazole must, according to EP 247 983, be separated from the enteric coating polymer(s) containing free carboxyl groups, which may otherwise cause degradation/discolouration of omeprazole during the coating process or during storage.

According to the present invention, the separating layer comprises a specific quality of HPC. This specific quality of HPC should preferably have a cloud point of at least 38°C determined by a Mettler instrument. The cloud point is determined in a mixed disodium hydrogenphosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3. The mixed solution used for the cloud point determination has a pH of 6.75 - 6.85. The concentration of HPC in the mixed solution is 1.0% (w/w) for the Mettler instrument. For more detailed information on the composition of the mixed solution, see below in the experimental section. Preferably, the HPC has a low viscosity, such as for instance below 400 mPas in a 5% (w/w) water solution at 25°C.

Alternatively, the quality of HPC may be determined by a method that correlates with the method described above, e.g. NIR spectrophotometry.

Additives such as plasticizers, colorants, pigments, fillers, anti-tacking, buffering agents, and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc, and other additives may also be included in the separating layer(s).

Enteric coating layer(s)

One or more enteric coating layers are applied onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in a suitable organic solvent. As enteric coating layer polymers one or more, separately or in combination, of the following polymers can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s). For environmental reasons, an aqueous coating process may be preferred. In such aqueous processes methacrylic acid copolymers are most preferred.

The enteric coating layers may contain pharmaceutically acceptable plasticizers to obtain desirable mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers. The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s). Additives such as dispersants, colorants, pigments, polymers e.g. poly(ethylacrylate, methylmethacrylate), anti-tacking and anti-foaming agents may also be included in the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acidic susceptible active substance.

To protect the acidic susceptible active substance, the enteric coating layer(s) preferably constitute(s) a thickness of at least approximately 10 μm. The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

The pellets or units covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipment such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the layering process.

Final dosage form.

The prepared pellets may be filled in hard gelatine capsules or compressed with suitable tablet excipients into a tableted multiple unit formulation, and the latter is preferred. Final dosage forms may also include but is not restricted to effervescent tablets, and combinations of omeprazole with other active ingredients, such as for instance antibacterial substances, NSAID(s), motility stimulating agents or antacids.

Experimental section.

Example 1: Test of omeprazole multiple unit tablets, in which the pellets are layered with different types of HPC used as a constituent of the separation layer (laboratory scale).

Omeprazole tablets with the following composition were prepared according to the description in WO 96/01623. Sugar spheres were spray layered in a fluidized bed with an aqueous suspension of omeprazole magnesium salt and HPMC. The prepared pellets were layered with a separating layer and thereafter enteric coated. Enteric coated pellets were mixed with tablets excipients and compressed into a multiple unit tablet.

The composition of the tested omeprazole tablets (20 mg strenght) was as follows.

NAME OF INGREDIENT	FORMULA (mg/tablet)
Omeprazole magnesium	20.6
Glyceryl monostearate	1.4
Hydroxypropylcellulose	4.8
Hydroxypropyl metylcellulose	4.6
Magnesium stearate	0.7
Methacrylic acid copolymer type C	27
Microcrystalline cellulose	220
Polysorbate 80	0.1
Polyvinylpyrrolidone crosslinked	4.6
Sodium stearyl fumarate	0.5
Sugar spheres	22
Talc	8.3
Triethyl citrate	8.2

Omeprazole multiple unit tablets prepared with a separating layer on the pellets which separating layer comprises HPC, of either quality i.e type A or type B. HPC of the two

types fulfill all requirements in the PhEur as well as the USP. However, the HPC of the two types differ with respect to some physical/chemical characteristics, e.g. cloud point.

The prepared tablets were tested according to the description below. The tablets, i.e. the pellets, were prepared from the same batch of omeprazole magnesium, and with the same enteric coating material. The release of omeprazole was tested on stored tablets after 0 month, and 6 months storage. The amount of released omeprazole within 30 minutes in a buffer solution was determined.

The tablets were pre-exposed to hydrochloric acid at 37°C for 2 hours. Thereafter the drug release in buffer solution pH 6.8 at 30 minutes was determined by liquid chromatography. The buffer solution pH 6.8 was a mixture of disodium hydrogenphosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3, pH should be between 6.75 and 6.85. The hydrochloric acid 0.1 M was prepared by dissolving 213 ml of conc. HCl in water and added with water to 25 000 ml. The disodium hydrogen phosphate solution 0.086 M was prepared by dissolving 382 g $Na_2HPO_4.2H_2o$ in water and dilute to 25 000 ml with water.

The stability testing was performed on (20 mg strength) tablets packed in plastic bottles with desiccant (the tablets were not covered by a tablet coat).

Results are shown in Figure 3a) and Figure 3b). Figure 3a) shows results with the HPC quality type A, i.e. a reference, and Figure 3b) shows results with HPC type B, i.e. according to the instant invention.

Example 2. Release of omeprazole from tablets comprising different types of HPC as a constituent of the separating layer.

Pilot scale batches (using HPC of type A: 6 batches, and type B: 2 batches) were manufactured in order to confirm the improvement found during the laboratory testing in Example 1. Results from stability studies are shown in Figure 1.

The comparison clearly indicates improved release rate stability for tablets containing HPC of type B relative to that of type A.

General compositions for omeprazole tablets (20-mg strength):

NAME OF INGREDIENT	FORMULA (mg/tablet)
Omeprazole magnesium	20.6
Colour iron oxide reddish-brown	0.3
Glyceryl monostearate	1.4
Hydroxypropylcellulose	4.8
Hydroxypropyl metylcellulose	15
Magnesium stearate	0.7
Methacrylic acid copolymer type C	27
Microcrystalline cellulose	220
Paraffin	0.2
Polyethylene glycol 6000	2.5
Polysorbate 80	0.1
Polyvinylpyrrolidone crosslinked	4.6
Sodium stearyl fumarate	0.5
Sugar spheres	22
Talc	8.3
Titanium dioxide	2.2
Triethyl citrate	8.2

The tablets were manufactured as described in example 1, with the additional step of a tablet coat comprising HPMC, PEG 6 000, and pigment.

Example 3. Cloud point determinations.

Omeprazole tablets were manufactured in laboratory scale as described in example 1.

Cloud point determinations of the HPC types in the Mettler instrument was conducted in the following way. The cloud point of the HPC types was determined in a mixed phosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3. The mixed solution used for the cloud point determination had a pH of 6.75 - 6.85. The concentration of HPC in the mixed solution was 1.0% (w/w). It is essential for the specificity of the cloud point determination that this system is used in the chosen instrument. The Mettler instrument comprises the following parts: Mettler FP90 Central processor, FP81C Measuring unit and ME-18572 boiling point tubes. A temperature range of 30.0 to 50.0°C was used and a heating rate of 1.0°C/min. The cloud point is defined as the temperature where the light transmission is 96%.

The results are shown in Figure 2.

Claims.

1. An enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, one of the single enantiomer of omeprazole and an alkaline salt of one of the single enantiomers of omeprazole, and the formulation comprises a core material that comprises the active ingredient optionally in admixture with an alkaline reacting compound, and the active ingredient is in admixture with one or more pharmaceutical acceptable excipients such as a binding agent, a filling agent and/or a disintegrating agent, and and on said core material a separating layer and an enteric coating layer, characterized in that a hydroxypropyl cellulose (HPC) with a cloud point of at least 38°C determined as the temperature where the light transmission of the system is 96%, is used as a consituent of the separating layer, and wherein the cloud point is determined in the following way: the HPC is dissolved in a concentration of 1.0% (w/w) in a mixed solution of disodium hydrogenphosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3 at a pH of 6.75-6.85.

2. A formulation according to claim 1, wherein the HPC has a cloud point of at least 40°C.

3. A formulation according to claim 1, wherein the HPC has a cloud point of at least 41°C.

4. A formulation according to claim 1, wherein the enteric coating layer comprises a methacrylic acid copolymer.

5. A formulation according to claim 1, wherein the HPC has a low viscosity.

6. A formulation according to claim 1, wherein the active ingredient is omeprazole.

7. A formulation according to claim 1, wherein the active ingredient is a magnesium salt of omeprazole.

8. A formulation according to claim 1, wherein the active ingredient is a magnesium salt of the (-)-enantiomer of omeprazole.

9. Use of a quality of hydroxypropyl cellulose (HPC) with a cloud point of at least 38°C at which the light transmission of a system is 96%, in the manufacture of an enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, one of the single enantiomer of omeprazole and an alkaline salt of one of the single enantiomer of omeprazole, and the formulation comprises a core material of the active ingredient optionally in admixture with an alkaline reacting compound, and the active ingredient is in admixture with one or more pharmaceutically acceptable excipients such as a binding agent, filling agent and/or disintegrating agent and on said core material a separating layer and an enteric coating layer, characterized in that the separating layer comprises a HPC with a cloud point as defined above and the cloud point is determined in the following way: the HPC is dissolved in a concentration of 1.0% (w/w) in a mixed solution of disodium hydrogenphosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3 at a pH of 6.75-6.85.

10. Use according to claim 9, wherein the HPC has a low viscosity.

11. A process for the manufacture of an enteric coated oral pharmaceutical formulation defined in claim 1, wherein the active substance mixed with a binding agent and optionally mixed with an alkaline reacting compound, is layered on a seed and formulated into a core material and on said core material a separating layer is coating layered, and thereafter an enteric coating layer is applied, characterized in that the separating layer comprises a hydroxypropyl cellulose HPC with a cloud point of at least 38°C at which the light transmission of a system is 96%, and the cloud point is determined in the following way:

the HPC is dissolved in a concentration of 1.0% (w/w) in a mixed solution of disodium hydrogenphosphate buffer 0.086 M and hydrochloric acid 0.1 M in the proportions 7:3 at a pH of 6.75-6.85.

12. Use of a pharmaceutical formulation as defined in any of claims 1 - 8 for the manufacture of a medicament for the treatment of gastrointestinal diseases.

13. A method for the treatment of gastrointestinal diseases in mammals including man by administrating to a host in need thereof a therapeutically effective dosage form defined in any of claims 1 - 8.

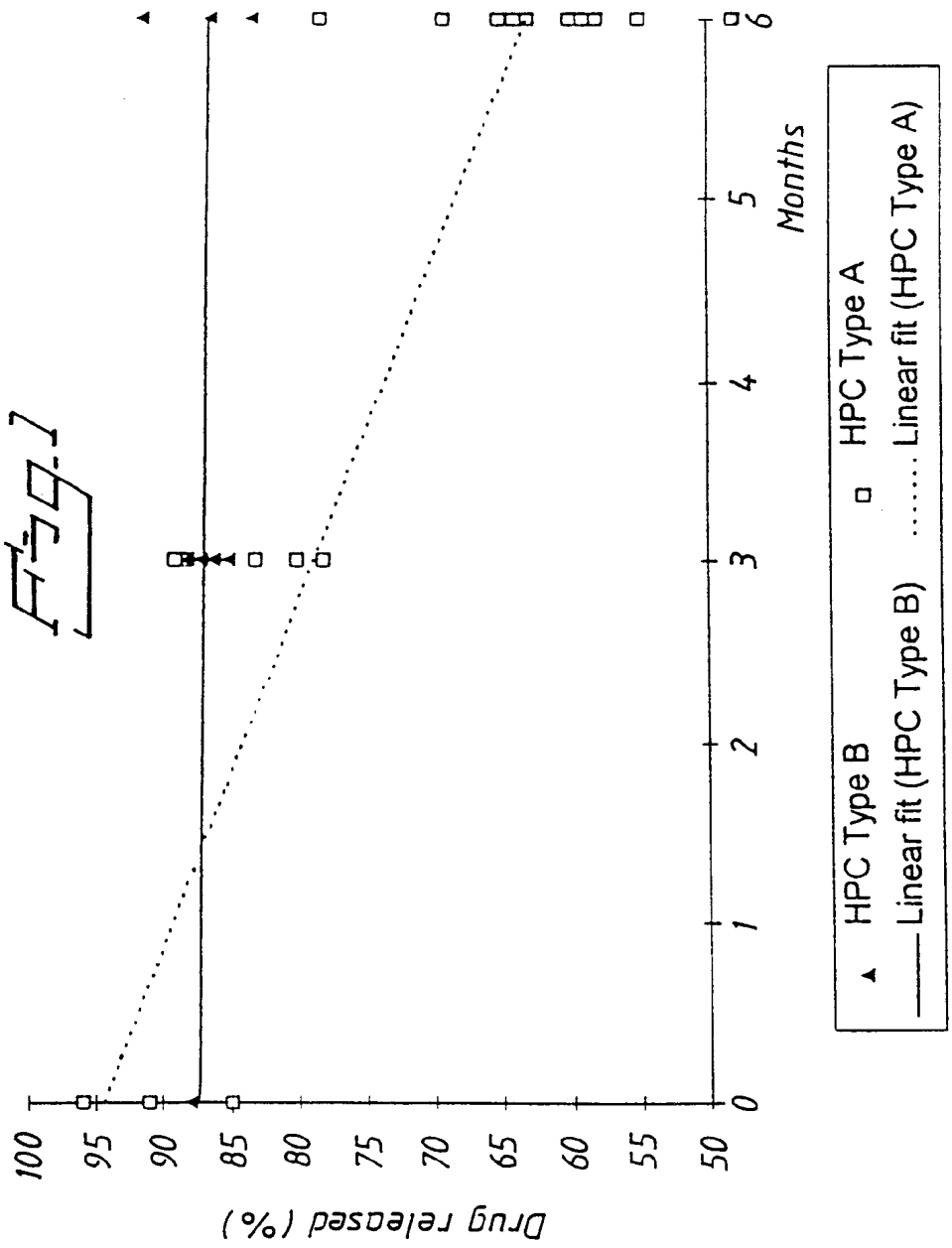
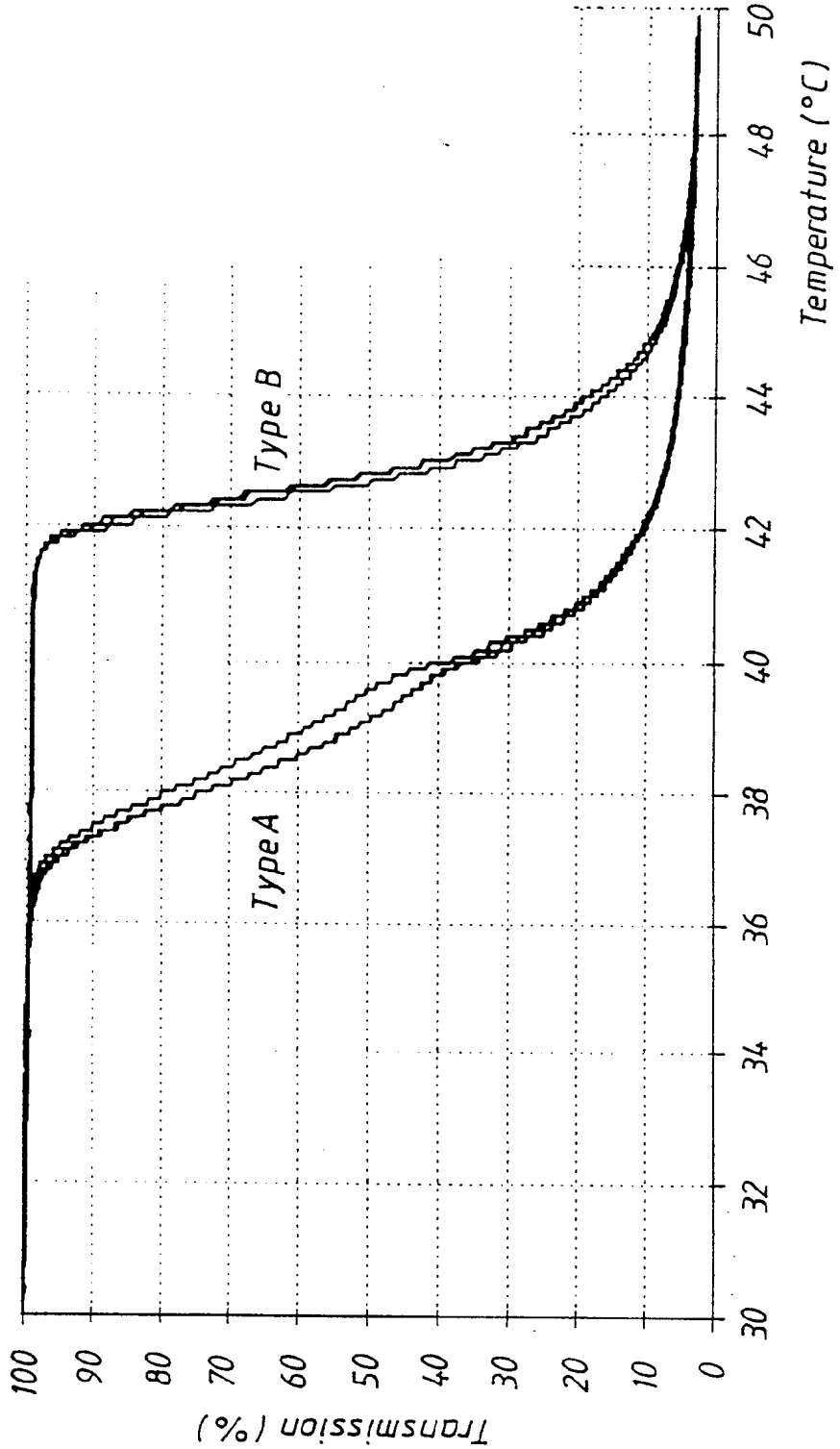


Fig 1
Drug released (%)
100
95
90
85
80
75
70
65
60
55
50
0
1
2
3
4
5
6
Months
HPC Type B
HPC Type A
Linear fit (HPC Type B)
Linear fit (HPC Type A)

Fig. 2


Type B
Type A
Transmission (%)
100
90
80
70
60
50
40
30
20
10
0
30
32
34
36
38
40
42
44
46
48
50
Temperature (°C)

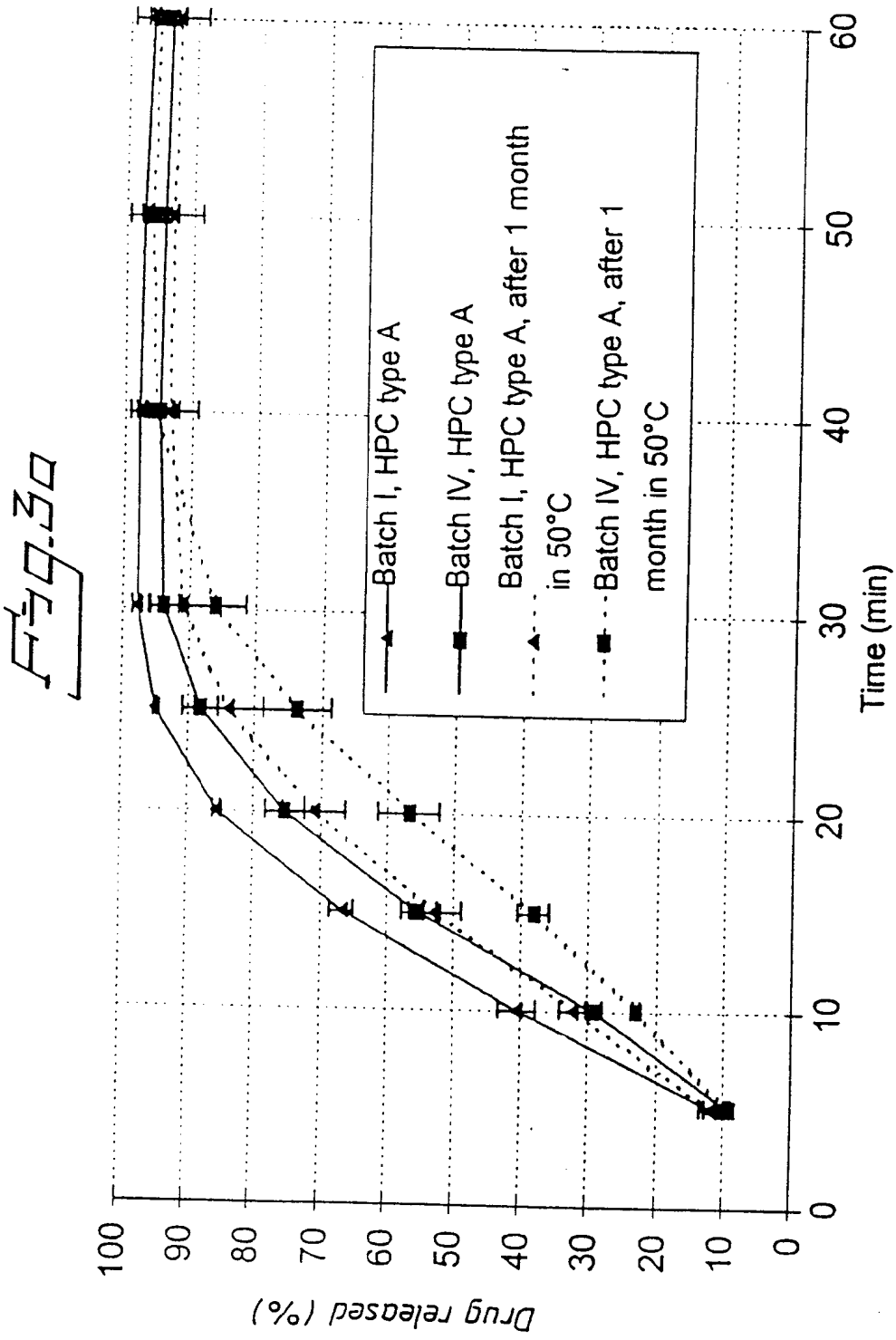


Fig.3a
Drug released (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
Time (min)
Batch I, HPC type A
Batch IV, HPC type A
Batch I, HPC type A, after 1 month in 50°C
Batch IV, HPC type A, after 1 month in 50°C

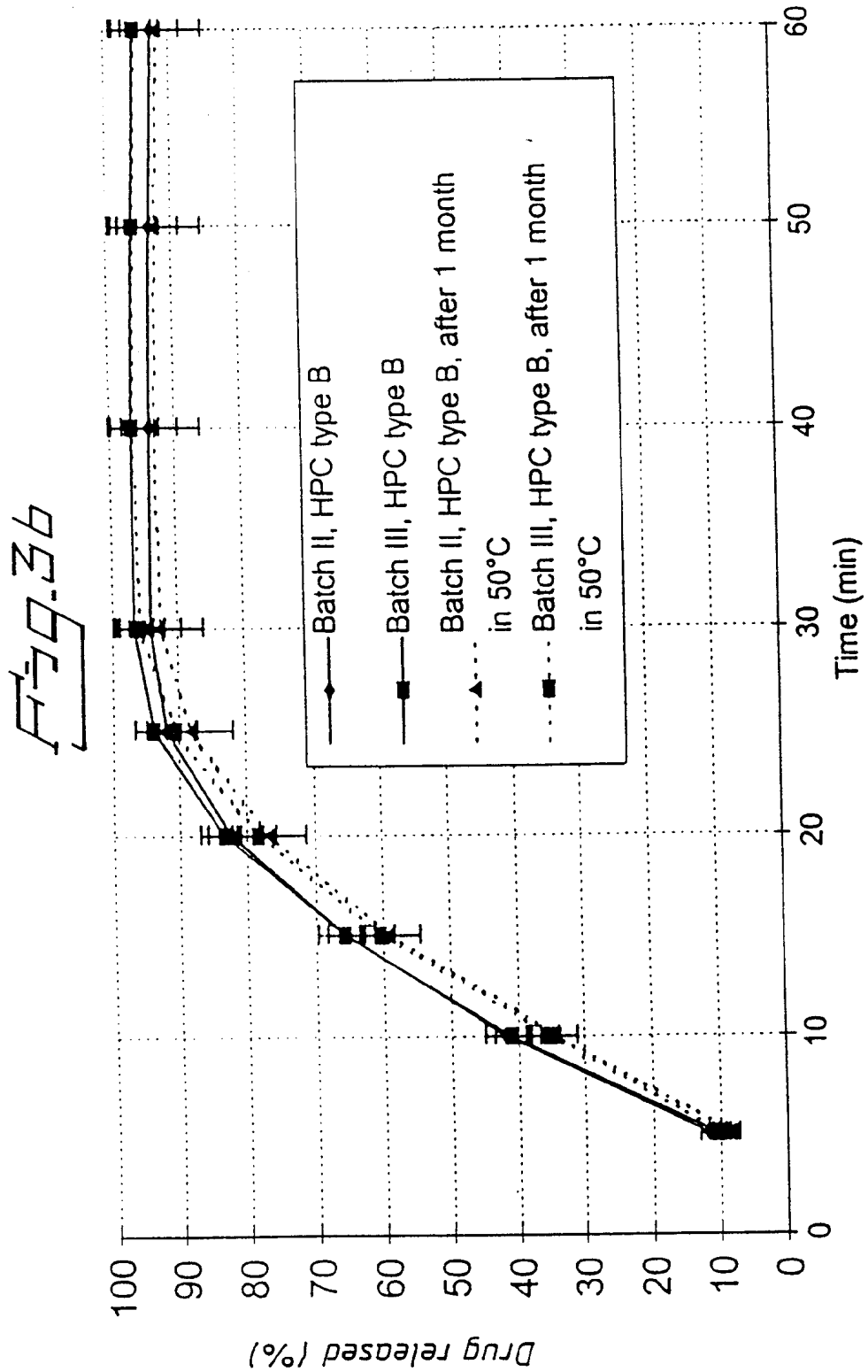


Fig. 3b
Drug released (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
Time (min)
Batch II, HPC type B
Batch III, HPC type B
Batch II, HPC type B, after 1 month in 50°C
Batch III, HPC type B, after 1 month in 50°C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01989

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/24, A61K 31/44, A61K 47/38
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9725066 A1 (ASTRA AKTIEBOLAG), 17 July 1997 (17.07.97), page 15, line 25 - page 16, line 5, examples 1-3, 6, 10 --	1-13
A	EP 0496437 A2 (AKTIEBOLAGET HÄSSLE), 29 July 1992 (29.07.92), example 2, claims -- --------	1-13

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 March 2000	10 -03- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01989

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 9901989

Claim 13 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 99/01989

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0496437 A2	29/07/92	SE 0496437 T3	
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INTERNATIONAL SEARCH REPORT

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International application No.
PCT/SE 99/01989

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		SK 116997 A	06/05/98

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 9/28, 31/41, 31/44

A2

(11) International Publication Number: **WO 00/28975**

(43) International Publication Date: 25 May 2000 (25.05.00)

(21) International Application Number: PCT/SE99/02093

(22) International Filing Date: 15 November 1999 (15.11.99)

(30) Priority Data:

9803953-0	18 November 1998 (18.11.98)	SE
9803952-2	18 November 1998 (18.11.98)	SE

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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ERICKSON, Magnus [SE/SE]; Astra Hässle AB, S–431 83 Mölndal (SE). GUSTAVSSON, Anders [SE/SE]; Astra Production Chemicals AB, S–151 85 Södertälje (SE). JOSEFSSON, Lars [SE/SE]; Astra Hässle AB, S–431 83 Mölndal (SE).

(74) Agent: ASTRAZENECA AB; Intellectual property, Patents, S–151 85 Södertälje (SE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

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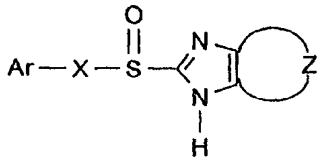

(I)

(57) Abstract

Process for the manufacturing of slightly soluble or less soluble alkaline salts of substituted sulphinyl heterocycles containing an imidazole moiety with formula (I), preferably alkaline salts of a proton pump inhibitor compound, wherein the process comprises the step of reacting the substituted sulphinyl heterocycle of formula (I) with a source of the cation in the presence of a base, characterized by a washing step in which the prepared alkaline salt of the substituted sulphinyl compound is washed with a basic aqueous solvent mixture. The obtained bulk drug substance resulting in a bulk product that in an aqueous suspension of the substituted sulphinyl heterocycle having a pH not significantly lower than that of a saturated water solution of the pure compound prepared. Alternatively, the process for manufacturing a pharmaceutical dosage form comprising the active substance could be adjusted. For instance the pH of an aqueous suspension of the active substance is adjusted to a pH not significantly lower than that of a saturated water solution of the pure compound. The processes are preferably useful in the manufacturing of omeprazole magnesium salt or magnesium salt of one of its single enantiomers used in pharmaceutical dosage forms.

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CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

IMPROVED CHEMICAL PROCESS AND PHARMACEUTICAL FORMULATION

Field of the invention.

The present invention relates to an improved process for the manufacturing of an alkaline salt of an acid susceptible proton pump inhibitor compound, such as a substituted sulphinyl heterocyclic compound containing an imidazole moiety. More specifically the invention is related to an improved process for the manufacturing of an alkaline salt of omeprazole or an alkaline salt of *(S)*-omeprazole, preferably magnesium salts of these compounds. The invention is also related to an improvement in the preparation of the pharmaceutical formulation and to products containing as the active ingredient a compound prepared by the claimed processes as well as the use of the products in medicine.

Background of the invention and prior art.

Substituted benzimidazoles such as for instance the compounds with the generic names omeprazole, lansoprazole, pantoprazole, rabeprazole and leminoprazole have properties making the compounds useful as inhibitors of gastric acid secretion. This class of compounds is known as proton pump inhibitors or H^+,K^+-ATPase inhibitors. There are a large number of patents and patent applications disclosing such proton pump inhibitors and processes for their manufacturing.

There is a general need in industry that pharmaceutically active compounds should be produced by processes giving products with properties, such as being easy to handle in full scale manufacturing and having good stability during storage, making them suitable for pharmaceutical preparations. The active substance, the drug, should also be presented in a form with such physico-chemical properties that are suitable for pharmaceutical manufacturing processing, and the drug should be released from the dosage form with a rate suitable for its intended pharmacological effect. Usually, it is the concern of the

formulator to develop dosage forms with the desired properties. However, to obtain a good formulation, it is beneficial and important that the active substance as such is prepared and presented in the most suitable form.

WO 95/ 01977 discloses a magnesium salt of omeprazole with a specific degree of crystallinity making the claimed product especially suitable for pharmaceutical formulations; this is also discussed in WO 95/01783.

An efficient process for the manufacture of a magnesium salt of omeprazole is described in WO 97/41114. This process comprises mixing and reacting omeprazole with a weak base and a magnesium source and optionally the reaction takes place in the presence of an organic solvent. After the reaction is completed, the product is preferably crystallised from the filtrate.

Other processes related to the manufacture of alkaline salts of proton pump inhibitors are for instance disclosed in WO 94/ 27988, in which the preparation of the single enantiomers of omeprazole and alkaline salts thereof is described.

The present invention provides improvements over the prior art processes. It represents especially an improvement of the process described in WO 97/41114.

A pharmaceutical dosage form suitable for proton pump inhibitor compounds is for instance described in WO 96/01624. Said patent application describes preparation of small enteric coating layered pellets comprising the active substance. These enteric coating layered pellets are compressed into tablets. Preferably, the preparation of pellets containing the active substance is performed by spray layering the active substance onto seeds, such as for instance sugar spheres, and thereafter applying the enteric coating layer, optionally after a separating layer has first been applied to separate the active substance from the finally applied enteric coating layer.

Proton pump inhibitor compounds are acid susceptible and with respect to the stability properties of these compounds, it is obvious that an oral solid dosage form must be protected from contact with the acidic gastric juice and that active drug must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

The rate of release of the drug from a pharmaceutical dosage form can influence the total extent of absorption of such a drug into the general circulation. Omeprazole and related drugs as well as dosage forms comprising these drugs have been investigated (See for instance Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). The marketing approval for these products specifies limits for the rate of release of the drug from the pharmaceutical dosage form.

Summary of the invention.

The present invention provides an improved process for the preparation of an alkaline salt of a substituted sulphinyl heterocycle containing an imidazole moiety and especially magnesium salts of substituted benzimidazole derivatives. The process results in a bulk product, which on addition of water, gives a suspension with a pH above a specified pH range. Said product is suitable for further processing into a pharmaceutical preparation. The release properties of such a pharmaceutical formulation comprising the new form of the active substance are improved. The claimed process provides especially a more suitable bulk drug product for pharmaceutical dosage forms, for intance a multiple unit tablet.

According to the improved process, an alkaline salt of a substituted sulphinyl heterocycle containing an imidazole moiety is prepared, and the process comprises a final step wherein a base is added to a washing solvent to adjust the pH of the solution, which solution is used in the final wash of the product. Preferably, a magnesium salt of the substituted sulphinyl heterocycle compound is prepared according to WO 97/41114, hereby included by reference, by mixing and reacting the substituted sulfinyl heterocycle compound with a weak base, preferably an amine or ammonia, and a magnesium source, such as an organic

or inorganic magnesium salt or a combination of such salts. Thereafter the crystallised and isolated magnesium salt product is washed with a basic aqueous solvent mixture.

The process may also be used to prepare other salts of substituted sulphinyl heterocycles containing an imidazole moiety, for instance slightly soluble or less soluble salts, preferably a multivalent salt such as a calcium salt, by the use of a calcium source or any other suitable source of that cation. Slightly soluble or less soluble salts are defined in compliance with the European Pharmacopiea (Edition 3) under the heading "General notice".

The present invention also provides an improved process for the preparation of a pharmaceutical dosage form by spray layering of the active substance onto seeds, such as for instance sugar spheres. The active substance is preferably an acid susceptible drug selected from an alkaline salt of a substituted sulphinyl heterocycle containing an imidazole moiety. The active substance is suspended in an aqueous solution of a macromolecular binding agent. The obtained suspension should have a pH not significantly lower than that of a saturated water solution of the pure drug substance.

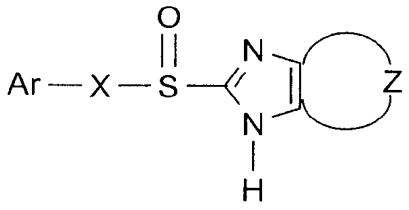
In one preferred embodiment, the claimed process relates to a process for the manufacturing of dosage forms comprising magnesium salts of substituted benzimidazole derivatives. More specifically, the process is related to the preparation of spray layered spheres with omeprazole magnesium in a water solution of a binding agent. The prepared pellets are covered by a separating layer and an enteric coating layer and filled into a capsule, or mixed with tablet excipients and compressed into a tableted multiple unit dosage form. Preferably, a tablet comprising a multiple of enteric coating layered units of omeprazole magnesium is prepared.

Brief description of the drawings.

Figure 1 shows the result from testing the rate of release of omeprazole from sugar spheres spray layered with a suspension of omeprazole magnesium as prepared according to Example 2. Three graphs refer to pellets prepared according to the present invention and two graphs refer to reference pellets.

Detailed description of the invention.

According to one aspect, the present invention provides a novel method of preparing a slightly soluble or less soluble alkaline salt of a substituted sulphinyl heterocycle containing an imidazole moiety with the following formula I



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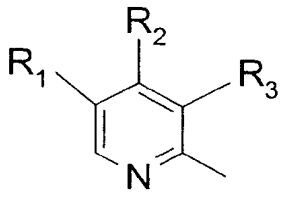

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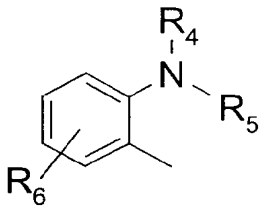

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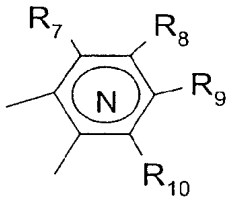

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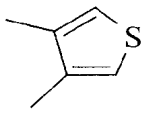

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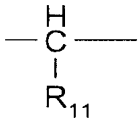

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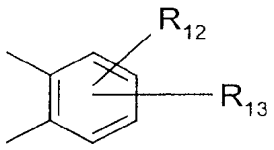


wherein

N inside the benzene ring of the benzimidazole moiety means that one of the carbon atoms substituted by R_7-R_{10} optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkylthio, alkoxy optionally substituted by fluorine, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6 is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_7 - R_{10} are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_7-R_{10} form ring structures which may be further substituted;

R_{11} is hydrogen or forms an alkylene chain together with R_3 and

R_{12} and R_{13} are the same or different and selected from hydrogen, halogen or alkyl,

and wherein alkyl groups, alkoxy groups and moieties thereof may be branched and straight C_1-C_9-chains or comprise cyclic alkyl groups, for example cycloalkylalkyl,

which process comprises the step of reacting the substituted sulphinyl heterocycle of Formula I with a source of the cation in the presence of a base. The process is characterised by a washing step in which the prepared alkaline salt of the substituted sulphinyl compound is washed with a basic aqueous solvent mixture. Such a preferred basic aqueous solvent mixture comprises for instance sodium hydroxide or ammonia, and preferably a solvent mixture comprising an alcohol, sodium hydroxide and water is used. The obtained bulk drug substance will, in an aqueous suspension of the substituted sulphinyl heterocycle of Formula I, have a pH equal to or above that of a saturated water solution of the pure alkaline salt of the substituted sulphinyl compound prepared.

In general, the present invention is applicable for the manufacturing of a slightly soluble or a less soluble alkaline salt of a substituted sulphinyl heterocycle containing an imidazole moiety. The invention is exemplified with the manufacturing of omeprazole magnesium salt.

Preferably, the magnesium salt of omeprazole is prepared by reacting omeprazole with a magnesium source in the presence of a weak base as described in WO97/41114, and the crystallised and isolated magnesium salt of omeprazole is washed with a basic aqueous solvent mixture.

One purpose of the present invention is to secure a pH not significantly lower than that of a saturated water solution of the pure compound when the manufactured bulk drug substance is suspended in water. Preferably, a suspension of omeprazole magnesium should have a pH of 9.5 or above in a 10 % (w/w) suspension of the bulk substance. To obtain a suitable

pH (as measured in a 10% suspension), a small amount of a base is added to increase the pH of the wash solution in order keep the pH of the bulk drug substance, in water, at a value not significantly lower than that of a saturated water solution of the pure compound. As an example, pKa for omeprazole magnesium is 8.8, and theoretically the pH of a saturated solution of omeprazole magnesium in water is about 9.6 at room temperature.

A suitable non-volatile base to be added to the wash solution is sodium hydroxide which is added in an amount of not exceeding 0.1% (w/w) of the solid omeprazole magnesium and preferably not more than approximately 0.02%. Ammonia is another suitable base for the claimed process.

According to a second aspect, the invention provides an improved method of preparing a pharmaceutical dosage form comprising the step of spray layering the active substance suspended in an aqueous solution of a binding agent onto seeds, preferably sugar spheres. A suspension of the active substance in water, preferably 10 - 50 % (w/w), is mixed with a binding agent, and optionally wet-milled. The pH of the suspension is controlled and adjusted before spray layering onto sugar spheres in a fluid bed. In the following example, a 25% suspension of omeprazole magnesium is prepared. The pH of the suspension is controlled and/or adjusted to a value not significantly lower than that of a saturated water solution of pure omeprazole magnesium by addition of a base. Suitable bases are for instance sodium hydroxide and ammonia, which are added in an amount needed to raise the pH to a desirable value.

A saturated water solution of omeprazole magnesium has, theoretically, a pH of 9.6, and the aqueous suspension of omeprazole magnesium and binding agent should have a pH of 9.4 or above, and more preferably a pH of 9.5 or above.

One of the purposes of the present invention is to secure a pH not significantly lower than that of a saturated water solution of the pure compound when making the suspension for

spray layering, i.e. when substance is suspended in an aqueous solution of the binding agent.

A suitable binding agent for the suspension of the active drug is a macromolecular agent, such as for instance celluloses such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropyl cellulose and carboxymethylcellulose sodium, polyvinyl pyrrolidone, gelatine, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. These binding agents can be used alone or in mixtures.

Furthermore, the suspension may comprise an alkaline reacting substance, in admixture with one or more pharmaceutically acceptable excipients. In addition to the binding agent, such excipients are for instance a disintegrating agent and/or a surface active ingredient.

The prepared spray layered units are enteric coated. Optionally the units are covered by a separating layer - before the enteric coating layer is applied - to separate the enteric coating layer from the active drug layer.

Suitable material and techniques for the seeds, enteric coating layering and the optional separating layer are known in the art. Preferred materials and techniques are for instance described in WO 96/01624, which is hereby included by reference.

Use of the invention

Proton pump inhibitors are generally known to be useful for inhibiting gastric acid secretion in mammals and man by controlling gastric acid secretion at the final step of the acid secretory pathway. Thus, in a more general sense, it may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcers and duodenal ulcers. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on non steroidal antiinflammatory drug (NSAID) therapy, in

patients with non ulcer dyspepsia, in patients with symptomatic gastro-oesophageal reflux disease, and in patients with gastrinomas. It may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, it may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these, as well as in the treatment or prophylaxis of inflammatory conditions in mammals, including man.

Prepared dosage forms comprising a drug substance prepared according to the invention are suitable for oral administration. The dose will depend on the nature and severity of the disease to be treated. The dose may also vary according to the age, body weight, and response of the individual patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. In the treatment of other conditions higher doses than average will be used.

Preferably, a dose of the proton pump inhibitor, for instance 1 - 500 mg is administered once a day. Suitable doses comprise for instance about 5 - 100 mg of the substance, and more preferably 5 - 80 mg. The dosage form may be administered together with other suitable drugs, such as antibacterial compound(s), NSAID(s), motility stimulating agents, and/or antacids. The dosage form may alternatively be in the form of a tableted effervescent multiple unit dosage form.

The invention is further described and discussed in the following by examples. The intention of the examples is not to limiting the scope of the invention which scope is defined by the enclosed claims.

Results and Discussion

It is beneficial for the pharmaceutical processing that the bulk drug substance suspended in water will produce a pH in the suspension which is not significantly lower than that of a saturated water solution of the pure compound. For instance, a suspension of omeprazole magnesium should have a pH of about 9.6.

The invention is illustrated by Example 1 and Reference Example A describing dissolution rate from pharmaceutical dosage forms comprising sugar spheres that are spray layered with an aqueous suspension of omeprazole magnesium. As the results show, a pH significantly lower than that of a saturated water solution of pure omeprazole magnesium in the washing step of the manufacturing process of the bulk drug substance may cause a low dissolution rate of omeprazole magnesium from the prepared pellets (Reference example A). These results can be compared with a formulation comprising pellets prepared from omeprazole magnesium with a pH not significantly lower than that of a saturated water solution of pure omeprazole magnesium in the washing step of the manufacturing process of the bulk drug substance (Example 1). The mechanism behind this lowering of the dissolution rate from the pharmaceutical dosage form, might depend on co-precipitation of small amounts of the non-ionized and less soluble forms of the substance (in this case non-salt forms of omeprazole) at the surface of the dried material. Such possible precipitation of omeprazole, non-salt form, will not disturb the dissolution rate from the pharmaceutical dosage form, if the pH in the aqueous suspension prepared from omeprazole magnesium and used for spray layering onto seeds is not significantly lower than that of a saturated water solution of pure omeprazole magnesium.

Furthermore, the invention is illustrated by Example 2 and Reference Example B. The prepared pellets were tested in USP dissolution apparatus with respect to release rate of omeprazole in phosphate buffer solution, pH 6.8; ionic strength I=0.16; temp 37°C; stirring rate 100 rpm. The release of omeprazole was followed by spectrophotometric determination (302 nm) and the results are presented in Figure 1.

The graphs show that the release of omeprazole can be increased by adjusting the pH to a value not significantly lower than that of a saturated water solution of the pure compound.

Example 1.

Examples of dissolution rate from pharmaceutical dosage forms manufactured from different batches of omeprazole magnesium prepared in accordance with the present invention.

Preparation:

Multiple unit tablets comprising enteric coating layered pellets of omeprazole magnesium were prepared in accordance with the description in WO 96/01623, see Example 2. Omeprazole magnesium was prepared in accordance with WO 97/41114,and the omeprazole magnesium was washed with a basic aqueous solvent mixture (methanol/water) containing a small amount of sodium hydroxide corresponding to 0.02% w/w of the omeprazole magnesium substance. The prepared omeprazole magnesium was used in the manufacturing of multiple unit tablets.

Analysis:

The pH-value of a water suspension (10% w/w) of omeprazole magnesium was measured (table I, column II), and the dissolution from manufactured tableted dosage forms of the respective batch of omeprazole magnesium was determined (table I, column III). The amount of omeprazole released within 30 minutes in a buffer solution was determined. The tablets were pre-exposed to 0.1 M hydrochloric acid at 37°C for 2 hours.

Table I: pH-value of the aqueous suspension of omeprazole-Mg, and dissolution of omeprazole from a multiple unit tablet prepared from such omeprazole-Mg

Batch	pH of omeprazole -Mg (10% w/w in water)	Dissolution (%, 30 min; n=6)

Susp. I*)	9.7	94 (101-93)
Susp. II*)	9.6	95 (93-97)
Susp. III**)	10.3	95 (92-99)
Susp. IV**)	10.1	93 (92-97)

*) pH >9.5 no addition of base needed in the wash solution.

**) Base added to the wash solution

Reference example A.

Examples of dissolution rate from pharmaceutical dosage forms manufactured from two different batches of omeprazole magnesium prepared without any addition of a base to the solvent used for washing of the omeprazole magnesium.

Preparation and analysis:

In accordance with Example 1, tableted dosage form were prepared from batches of omeprazole magnesium having a pH-value of a 10% w/w suspension in water significantly lower than that of a saturated solution of the pure compound and the corresponding dissolution rate from manufactured tablets was measured.

Table A: pH-value of the aqueous suspension of omeprazole-Mg, and dissolution of omeprazole from a multiple unit tablet prepared from such omeprazole-Mg

Batch	pH of omeprazole -Mg (10% w/w in water)	Dissolution (%, 30 min; n=6)
Susp. A I	9.2	77 (81 - 73)
Susp. A II	9.2	71 (69 - 73)

The results from Example 1 and Reference Example A show that the addition of a base to the wash solution in the final washing step in the manufacturing of omeprazole magnesium, to increase the pH (resulting in an aqueous suspension of the omeprazole magnesium having a pH not significantly lower than that of a saturated water solution of pure omeprazole magnesium), has an influence on the dissolution rate from a tableted enteric coated pharmaceutical dosage form comprising said omeprazole magnesium.

Example 2

Core material comprising omeprazole magnesium was prepared by spray layering a suspension of omeprazole magnesium onto sugar sphere seeds (0.25 - 0.35 mm) in a fluid bed apparatus.

Composition of the suspension:

omeprazole magnesium	25.0 % (w/w)
hydroxypropyl methylcellulose	3.75 % (w/w)
water	71.25 % (w/w)

The pH of the suspension was controlled and adjusted by addition of a suitable amount of sodium hydroxide or ammonia to pH 9.6 - 9.7. Thereafter, 400 - 600 g of suspension was sprayed onto 100 -150 g sugar spheres (0.25 - 0.35 mm). Three prepared experimental pellets were tested as described below, and results are shown in Figure 1.

Reference example B

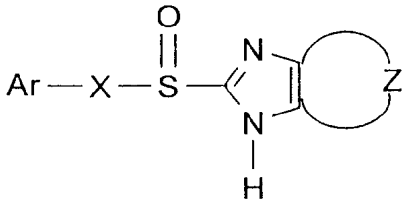
Core material comprising omeprazole magnesium was prepared by spray layering a suspension of omeprazole magnesium onto sugar sphere seeds (0.25 - 0.35 mm) in a fluid bed apparatus as described in Example 2. The suspension of omeprazole magnesium had a

pH value of 8.7 in both experiments. The prepared pellets were tested as described below, and the results are shown in Figure 1.

The prepared pellets were tested in USP Dissolution Apparatus No 2 (paddle) with respect to release rate of omeprazole in phosphate buffer solution pH 6.8; ionic strength 0.16; temperature 37°C; stirring rate 100 rpm. The release of omeprazole was followed by spectrophotometric determination (302 nm).

Patent claims

1. A process for the manufacturing of slightly soluble or less soluble alkaline salts of substituted sulphinyl heterocycles containing an imidazole moiety with formula I, in racemic form, one of the single enantiomer or an enantiomeric enriched form



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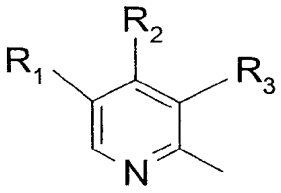

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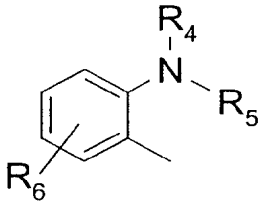

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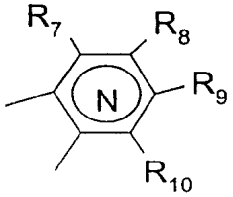

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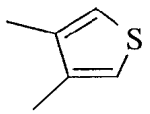

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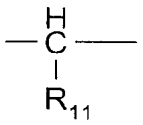

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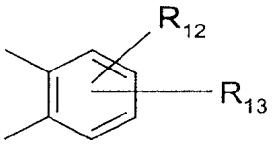


wherein

N inside the benzene ring of the benzimidazole moiety means that one of the carbon atoms substituted by R_7-R_{10} optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkylthio, alkoxy optionally substituted by fluorine, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl,

R_6 is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_7 - R_{10} are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_7-R_{10} form ring structures which may be further substituted;

R_{11} is hydrogen or forms an alkylene chain together with R_3 and

R_{12} and R_{13} are the same or different and selected from hydrogen, halogen or alkyl,

and wherein alkyl groups, alkoxy groups and moieties thereof may be branched and straight C_1-C_9-chains or comprise cyclic alkyl groups, for example cycloalkylalkyl,

which process comprises the step of reacting the substituted sulphinyl heterocycle of Formula I with a source of the cation in the presence of a base, characterised by a washing step in which the prepared alkaline salt of the substituted sulphinyl compound is washed with a basic aqueous solvent mixture.

2. The process according to claim 1, wherein the slightly soluble or less soluble alkaline salts of Formula I is a magnesium salt of substituted sulphinyl heterocycles containing an imidazole moiety with Formula I.

3. The process according to any of claims 1 and 2, wherein the pH of the basic aqueous solvent mixture is adjusted by addition of a base to a pH resulting in a bulk product, that in an aqueous suspension of the substituted sulphinyl heterocycle, having a pH of not more than 0.2 pH-units lower than that of a saturated water solution of the pure alkaline salt of the substituted sulphinyl compound.

4. The process according to claim 3, wherein the base is sodium hydroxide or ammonia.

5. The process according to any of claims 1 - 4, wherein a magnesium salt of omeprazole is prepared.

6. The process according to claim 5, wherein the base added to the wash solution is sodium hydroxide in an amount of not exceeding 0.1% (w/w) of the solid omeprazole magnesium.

7. The process according to claim 5, wherein the base added to the wash solution is sodium hydroxide in an amount of not exceeding 0.02% (w/w) of the solid omeprazole magnesium.

8. The process according to any of claims 1 - 4, wherein a magnesium salt of the (*S*)-omeprazole is prepared.

9. A pharmaceutical dosage form comprising a drug substance prepared according to any of claims 1 - 8 for use in medicine.

10. The use of a pharmaceutical dosage form comprising a drug substance prepared according to any of claims 1 - 8 for the treatment of gastrointestinal diseases.

11. Method of treatment of gastrointestinal diseases by the administration to a patient in the need thereof of a pharmaceutical dosage form comprising a drug substance prepared according to any of claims 1 - 8.

12. An improved process for the manufacture of a pharmaceutical dosage form comprising as active substance a compound manufactured according to any of claims 1 – 8, the process comprises the step of spray layering the active substance in the form of a suspension of the substance in a water solution of a binding agent onto seeds, wherein the pH of the aqeuous suspension of the active substance is adjusted to a pH of not more than 0.2 pH-units lower than that of a saturated water solution of the pure alkaline salt of the substituted sulphinyl compound.

13. The process according to to claim 12, wherein the suspension of the active substance in a water solution of a binding agent is wet-milled to a micronised suspension.

14. The process according to any of claims 12 – 13, wherein the pH is adjusted by addition of a base.

15. The process according to claim 14, wherein the base is sodium hydroxide or ammonia.

16. The process according to any of claims 12 – 15, wherein the active substance is a magnesium salt of omeprazole.

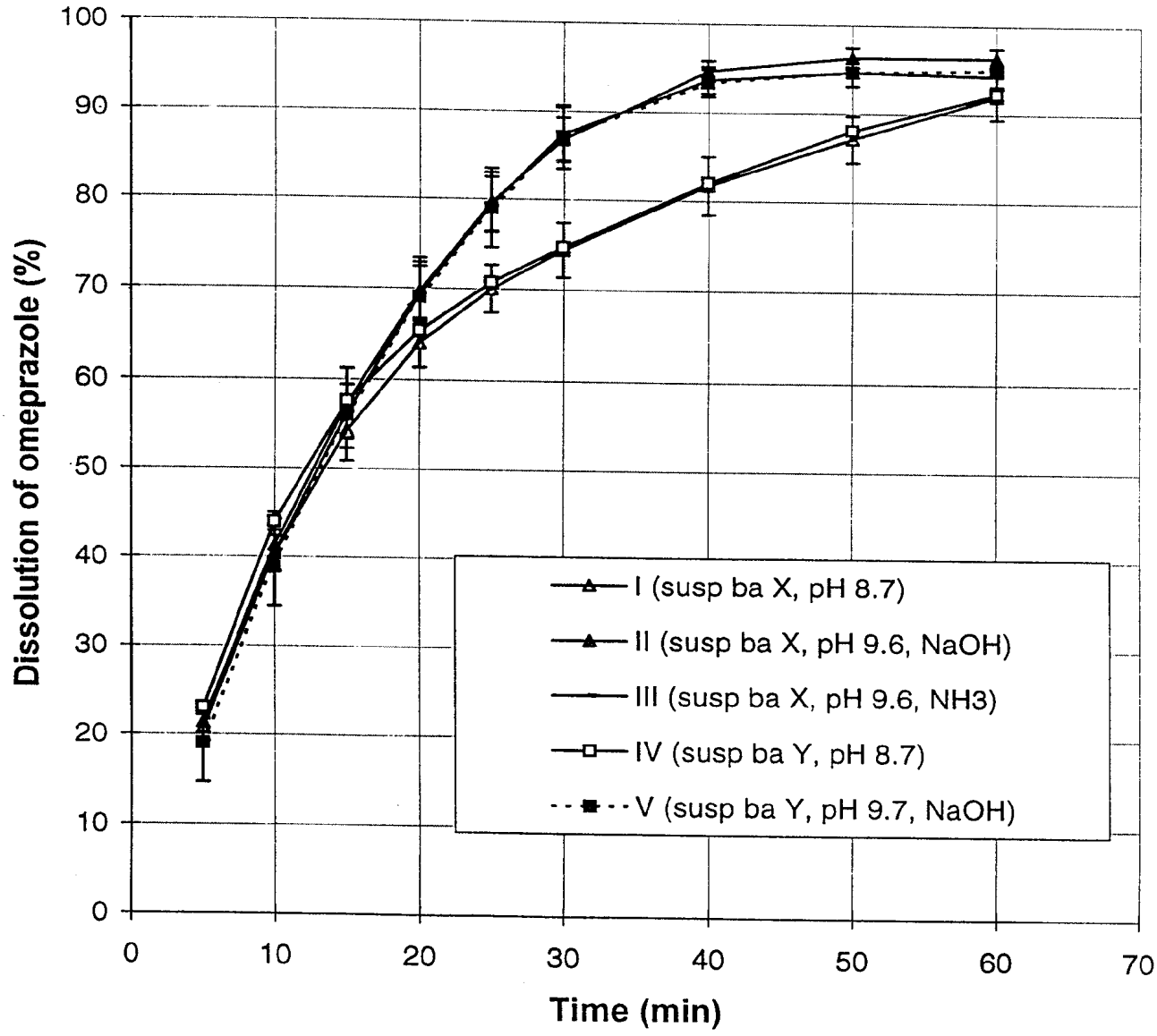
17. The process according to any of claims 12 – 15, wherein the active substance is a magnesium salt of *(S)*-omeprazole.

18. A pharmaceutical dosage form according to any of claims 12 - 17 for use in medicine.

19. The use of a pharmaceutical dosage form according to any of claims 12 - 17 for the treatment of gastrointestinal diseases.

20. Method of treatment of gastrointestinal diseases by the administration to a patient in the need thereof of a pharmaceutical dosage according to any of claims 12 - 17.

Fig.1


Dissolution of omeprazole (%)
Time (min)
0
10
20
30
40
50
60
70
80
90
100
I (susp ba X, pH 8.7)
II (susp ba X, pH 9.6, NaOH)
III (susp ba X, pH 9.6, NH3)
IV (susp ba Y, pH 8.7)
V (susp ba Y, pH 9.7, NaOH)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 9/14, 31/41, 31/44, 31/165

A1

(11) International Publication Number: **WO 00/30612**

(43) International Publication Date: 2 June 2000 (02.06.00)

(21) International Application Number: PCT/SE99/02152

(22) International Filing Date: 22 November 1999 (22.11.99)

(30) Priority Data:
9804003–3 23 November 1998 (23.11.98) SE

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(74) Agent: ASTRAZENECA AB; Intellectual Property, Patents, S–151 85 Södertälje (SE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: A METHOD OF PRODUCING DRUG PARTICLES

(57) Abstract

A method of preparing drug particles of a substance which are susceptible to degradation by the use of a fluid gas technique.

FOR THE PURPOSES OF INFORMATION ONLY

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A METHOD OF PRODUCING DRUG PARTICLES

FIELD OF THE INVENTION

The present invention relates to a method for the production of drug particles. More specifically, the invention relates to a method for the production of drug particles having minimal amount of degradation products when obtained by a fluid gas technique process. The invention also relates to such particles when obtained by the method of the invention.

BACKGROUND OF THE INVENTION

The strategy for the pharmaceutical formulation work of a given drug depends on different factors. Ultimately, these factors emanate from 1) the therapeutic needs, 2) the physical chemical properties of the drugs, and 3) the influence from the biological environment where the formulation will release its contents. Thus, both technical and biopharmaceutical considerations will contribute to a successful therapy.

However, improved drug administration will also be achieved by development of microparticles. The particle size of a poorly soluble drug is often the key role to a beneficial bioavailability. In this development, particles having a high content of active substance, with narrow particle size distribution are desired. These requirements of the micronization process is not always fulfilled, using conventional size-reduction techniques, such as traditional milling or grinding. When subjected to conventional micronization techniques, solids, sensitive to thermal degradation or chemical reactions may be degraded.

The use of supercritical fluids as transport media in the formation of fine powders is a known micronization technique (Krukonis V, AlChE meeting, Paper 140f, November (1984) San Francisco; King M L, Larson K A, Biotechnology Progress, vol. 2, No. 2 (1986) 73-82). One of the advantages using a supercritical fluid as a solvent is that organic solvents can be avoided. Generally, when using supercritical techniques, there are less

residual solvents in the produced powder. The operating temperatures are usually low, compared to conventional techniques and the particle size of the produced powder is small, having a narrow distribution. This results in smaller dose variations, when using these microparticles in a pharmaceutical formulation.

There are several techniques today that uses the properties of a supercritical fluid to produce particles. This has been reported in articles which are presented in the prior art section.

Supercritical fluids are generally considered to be chemically inert. This is crucial in the process of producing particles, using supercritical fluid crystallisation techniques. Still, there are some differences among different supercritical fluids in their interaction with other compounds (Prauznitz J M et al., Molecular Thermodynamics of fluid-phase equilibria, 2nd Ed. (1986) Prentice-Hall Inc., Englewood Cliffs, N.J.; McHugh M, Krukonis V, Supercritical fluid extraction, 2nd Ed. (1994) Chap. 5, Butterworth-Heinemann).

In supercritical fluid technology, the most commonly used fluid is carbon dioxide. Carbon dioxide may induce undesirable interaction with other components used in the process. It is in place to emphasize that a fluid gas (i.e material in its supercritical and near supercritical state as well as compressed gases), such as carbon dioxide, fluorocarbons, chlorocarbons, fluorochlorocarbons, etc., or mixtures thereof, may interact with any components used in the process, such as solvent(s) or substance(s), which may cause degradation of the final product.

A substance may have water included in the crystal lattice. Using supercritical fluid technology, both substance and water are then needed in the process to get the right crystal modification of the product. Water may produce acidic compound(s) when interacting with for instance carbon dioxide, sulfur dioxide, nitrogen oxide, and sulfur hexafluoride. These acid compounds may cause degradation of the substance(s) to be precipitated.

In the presence of an oxidizing agent, such as carbon dioxide (Chang C J, Randolph A D, AlChE Journal., vol. 35, No. 11 (1989) 1876-1882), alcohols may contribute to acidic conditions in an equilibrium reaction.

A fluid gas dissolved in a solvent may produce acidic conditions. Fluid gas as producing acidic conditions are for instance carbon dioxide, sulfur dioxide, nitrogen oxide, sulfur hexafluoride, fluorocarbons, chlorocarbons, and fluorochlorocarbons. Solvent producing acidic conditions are for instance alcohols, and water.

PRIOR ART

There are several techniques used today which are based on supercritical technology. One is known as rapid expansion of supercritical solutions (RESS) and another is known as gas antisolvent precipitation (GAS). In the GAS technique a substance of interest is dissolved in a conventional solvent, whereafter a supercritical fluid such as carbon dioxide is introduced into the solution, leading to rapid expansion of the volume of the solution. As a result, the solvent power decreases dramatically over a short period of time, leading to nucleation and precipitation of particles, [Gallager et al., ACS Symposium series 406, Chap. 22 (1989) 334-354; Tom J W, Debenedetti P G, J. of Aerosol Sci., 22 (1991) 555-584; Debenedetti P G et al., J. Controlled Release, 24 (1993) 27-44; WO 90/03782]. A modification of the GAS process has been developed (WO 95/01221 and WO 96/00610) called the SEDS (solution enhanced dispersion by supercritical fluid) process, which uses the concept of co-introducing a supercritical fluid and a substance in solution or suspension into a particle formation vessel.

Schmitt et al. (Schmitt et al., AlChE Journal, 41 (1995) 2476-2486) describes the use of carbon dioxide and ethane as a supercritical fluid. By injecting a solute solution into an agitated volume of supercritical or near supercritical fluid, rapid crystallisation is reported to be obtained.

Different interactions using different supercritical fluids has been reported in articles: Chang and Randolph (Chang C J, Randolph A D, AlChE J., vol. 35, No. 11 (1989), 1876-1882) who describes the dissolution of β-carotene in supercritical carbon dioxide, supercritical ethane and supercritical ethylene. When using supercritical carbon dioxide as solvent, β-carotene-related epoxide was produced (RESS technique).

EP 322 687 discloses a process wherein a fluid gas is used to obtain a substance/carrier formulation.

Fulton et al. (Fulton J L, Yee G G, Smith R D, J. Am. Chem. Soc., 113 (1991) 8327-8334; Fulton J L, Yee G G, Smith R D, Langmuir, 8 (1992) 337-384) measured the degree of intermolecular hydrogen bonding between solute molecules in different supercritical fluids and in liquid heptane. These articles describes interactions between different supercritical fluids and solute molecules.

WO 97/14407 discloses the use of supercritical ethane for beta-carotene in rapid expansion from supercritical solution.

None of the documents mentioned above discloses use a specific supercritical fluid to protect from degradation a acid labile substance in hydrate form, when applied to a supercritical technique process.

DISCLOSURE OF THE INVENTION

It has now surprisingly been found that, in a fluid gas technique process, an acid labile substance being in hydrate form can be obtained without substantial degradation of the substance.

The novel method according to the invention is based on the finding that by using specific fluid gases in the process, substances which are acid labile and in hydrate form are

insignificantly influenced by the process. The result is particles having small amount of degradation products.

An object of the invention is thus to provide a method for preparing drug particles of substances, which are acid labile and in hydrate form and which method does not substantially negatively influence the substance applied to the method.

A further object of the invention is to provide the drug particles of substances, which are acid labile and in hydrate form by use of the method of the invention.

Substances on which the method according to the present invention could be applied are acid labile substances, substances containing crystal water, etc.

An acid labile substance is defined as a substance that is degraded when exposed to an acidic environment.

An acid labile substance is defined in the present specification as a substance that generates degradation products 0.2% or more of the initial weight of the substance when applying CO_2 as fluid gas during processing time, typically 8-24 hours, than is generated when applying any of the fluid gases according to the invention.

The substances can be, but are not limited to pharmaceutically active substances such as: hydrates of omeprazole, omeprazole Mg, omeprazole Na, (S)-omeprazole, (S)-omeprazole Mg, (S)-omeprazole Na, formoterol fumarate etc.

The fluid gas techniques used for the formation of the pharmaceutical product, with the active substance(s) are antisolvent techniques such as, but not limited to, SEDS, ASES (aerosol solvent extraction system), SAS (supercritical antisolvent), GAS and PCA (precipitation with compressed fluid antisolvent).

The particular fluid gas used in the method according to the present invention is selected from the group consisting of saturated or unsaturated low molecular weight hydrocarbons, xenon, dimethyl ether and mixtures of these gases. Saturated or unsaturated low molecular weight hydrocarbons are such as having 1 - 6 carbon atoms, for instance ethane and propane. Particularly preferred is ethane.

The definition of fluid gas in this application includes material in its supercritical and near supercritical state as well as compressed gases.

The method according to the invention of producing particles of substances which are susceptible to degradation is characterized in that it comprises the following steps:

a) Dissolution of the substance or substances in a solvent or a mixture of solvents.

The solvents that can be used are alcohols, ethers, ketones, esters, alkanes, halides etc., or mixtures thereof. Examples of such solvents are methanol, ethanol, isopropanol, n-propanol, methylene chloride, acetone, ethylacetate, ethylether, or mixtures thereof. Also other solvents used as such or in mixtures with these above or in between can be but are not limited to water, ammonia and dimethylsulfoxide (DMSO).

Solvents such as those mentioned above can be added to the process as modifiers or co-solvents. By adding modifiers to the process the physical properties of the fluid gas is altered. For example, this may be done to alter the solubility of substance(s) or its solvent(s) in the fluid gas. If the amount of water used in the process is higher than the maximum amount to obtain a single phase system in the process, a modifier might be needed. The modifier is mixed with the fluid gas, before contacting the solution or co-introduced with the solution just before contact with the fluid gas. As modifiers or co-solvents should be mentioned alcohols, ethers, ketones, esters, alkanes, halides etc., or mixtures thereof. Examples of such modifiers or co-solvents are methanol, methylene

chloride, ethylacetate, acetone or any of the others mentioned as examples of solvents above.

The substance is dissolved, dispersed and/or solubilised in a solvent, where water often is one of the components (but not necessarily). If the substance which is susceptible to degradation contains crystal water, the amount of water used as solvent is adjusted to the amount of crystal water needed to crystallise the substance, and to the solubility of water in the fluid gas.

b) Using the fluid gas technique to form the particles comprising one or more substance(s).

Relevant examples are given in the Experimental section.

The product containing the drug substance(s) according to this invention can be used for pharmaceutical purposes such as therapeutic, prophylactic and diagnostic purposes.

Formulations based on this invention can be used for different administrations routes, such as by oral, nasal, rectal, buccal, intraocular, pulmonary, transdemal, parenteral such as intravenous, subcutaneous, intramuscular or as an implantate.

The particles produced by the method of this invention can be used in pharmaceutical formulations in the form of a solid, semisolid, liquid dispersion, or solutions prepared by use of well known pharmaceutical techniques, such as blending, granulation, wet or dry milling, compaction, coating, etc. Further, the formulation may be monolithic, such as tablets, or capsules, or in the form of multiple formulations administrated in a tablet, capsule, or sachets.

EXPERIMENTAL SECTION

Material and methods

In this section, the materials, analytical methods and preparation techniques used in the following examples are described.

MATERIAL

Omeprazole magnesium, tetrahydrate (Astra AB, Sweden), (S)-omeprazole magnesium, trihydrate (Astra AB, Sweden), formoterol fumarate, dihydrate (Astra AB, Sweden) were used as active substances. Ethanol (99.5 %), methanol (99.8%), ammonia (33%), acetone (99.5%) and water were used as solvents. Carbon dioxide (food grade) and ethane (99.0%) were used as antisolvents (AGA gas AB).

ANALYSIS OF PARTICLES

High-Perfomance Liquid Chromatography (HPLC)

Identification and quantification of degradation products were determined using HPLC technique.

The amount of degradation products was calculated from the chromatograms as area-%. Thus, 0.2% area-procent means that the amount of degradation products was 0.2% of the initial weight of the substance.

Powder X-ray Diffraction (pXRD)

The crystal characteristics of the produced powder were studied in an X-ray powder diffractometer (Siemens D5000, Germany).

Fourier Transform-Raman (FT-Raman)

The crystal characteristics of the produced powder were studied, using FT-Raman spectroscopy (FT-Raman, PE2000, UK).

Thermogravimetric analysis (TGA)

The amount of crystal water in the produced powder was studied using TGA (Mettler-Toledo TA8000, Switzerland).

PREPARATION OF PARTICLES

Particles were prepared in a modified SEDS equipment (Bradford Particle Design Limited, UK) from a solution, containing substance(s).

The solution and the antisolvent were introduced into a coaxial nozzle, which was located inside a pressure vessel. Under controlled pressure and temperature conditions, the antisolvent extracts the solvent from the solution droplets. The concentration of the solute in the droplets is thereby increased, leading to rapid particle formation. The particles were collected in a vessel, while the antisolvent and the extracted solvent emerged through a back pressure regulator.

The nozzle used was a two component nozzle, with an opening of 0.2 mm in diameter. In the two component nozzle the supercritical fluid passes through the inner passage, while the solution passes through the outer passage.

Example 1. Omeprazole magnesium, tetrahydrate

Omeprazole magnesium was dissolved in ethanol, in an ultrasonic bath. After dissolution, water or ammonia were slowly added to the solution. Several compositions of the omeprazole magnesium solution were used in different experiments (Table 1).

Table 1. Compositions of the omeprazole magnesium solution.

Composition no.	Solution in experiments	Concentration (w/v%)*	Ethanol (99.5%) (v%)	Water (v%)	Ammonia (33%) (v%)
1-1	1-1a	1.0	97.0	-	3.0
1-1	1-1b	1.0	97.0	-	3.0
1-2	1-2b	1.0	97.0	3.0	-
1-3	1-3a	0.625	98.25	-	1.75
1-3	1-3b	0.625	98.25	-	1.75
1-4	1-4b	0.625	98.25	1.75	-

* (w/v%) weight/volume%

The solution (several compositions) was co-introduced with the antisolvent (carbon dioxide or ethane) in the coaxial nozzle under controlled temperature and pressure (Table 2).

Table 2. SEDS processing of different solutions, using different antisolvents.

Experiments	Antisolvent	Pressure (bar)	Temperature (°C)	Flow rate antisolvent (ml/min)	Flow rate solution (ml/min)	Degradation products (a%)*
1-1a	CO_2	80	60	9.0	0.10	0.5
1-1b	ethane	80	60	9.0	0.10	0.2
1-2b	ethane	80	60	9.0	0.10	0.2
1-3a	CO_2	100	65	7.5	0.15	0.4
1-3b	ethane	100	65	7.5	0.15	0.2
1-4b	ethane	100	65	7.5	0.15	0.1

* (a%) area %

The particles made from a solution, using ethanol and ammonia (33 %) as solvents (compositions 1-1 and 1-3 in Table 1), were crystallised as omeprazole magnesium

tetrahydrate, when ethane was used as antisolvent (pXRD, TGA, FT-Raman). The degradation products were 0.2 area % in sample 1-1b and 1-3b (HPLC).

When ethanol and water were used as solvents (composition 1-2 and 1-4 in Table 1), the material still crystallised as omeprazole magnesium tetrahydrate, when ethane was used as antisolvent (pXRD, TGA FT-Raman). The degradation products were 0.2 area % in 1-2b and 0.1 area % in 1-4b (HPLC).

When using carbon dioxide as antisolvent the produced particles consisted of anhydrous omeprazole (composition 1-1 and 1-3 in Table 1) (pXRD, TGA, FT-Raman). The degradation products were 0.5 area % in 1-1a and 0.4 area% in 1-3a (HPLC).

The amount of degradation products are summerized in Table 2.

The experiments clearly show that by using the method of this invention, a better product (i.e lower amount of degradation products) is obtained with ethane as anti-solvent.

Example 2.(S)-omeprazole magnesium, trihydrate

(S)-omeprazole magnesium was dissolved in ethanol, in an ultrasonic bath. After dissolution, water was slowly added to the solution. One composition of the s-omeprazole magnesium solution was used in the experiments (Table 3).

Table 3. Compositions of the (S)-omeprazole magnesium solution.

Composition no.	Solution in experiments	Concentration (w/v%)	Ethanol (99.5%) (v%)	Water (v%)
2-1	2-1a	1.0	97.0	3.0
2-1	2-1b	1.0	97.0	3.0

The solution was co-introduced with the antisolvent (carbon dioxide or ethane) in the coaxial nozzle under controlled temperature and pressure (Table 4).

Table 4. SEDS processing of solution, using different antisolvents.

Experiments	Antisolvent	Pressure (bar)	Temperature (°C)	Flow rate antisolvent (ml/min)	Flow rate solution (ml/min)	Degradation products (a%)
2-1a	CO_2	150	45	9.0	0.1	2.1
2-1b	ethane	150	45	9.0	0.1	0.3

The particles made from a solution, using ethanol and water as solvents, were crystallised as (S)-omeprazole magnesium hydrate, when ethane was used as antisolvent (pXRD, FT-Raman). Sample 2-1b was found to contain about 3.4 moles of hard bound water (TGA). The pattern of weight loss suggests that the sample is crystalline. The degradation products in 2-1b were 0.3 area % (HPLC).

The particles formed, using carbon dioxide as antisolvent were amorphous. The analysis shows no crystalline content in sample 2-1a (pXRD, FT-Raman). The pattern of weight of loss suggests that the sample is amorphous (TGA). The degradation products were 2.1 area % in 2-1a (HPLC).

The amount of degradation products are summerised in Table 4.

The experiments clearly show that by using the method of this invention, a better product is obtained with ethane as anti-solvent.

Example 3. formoterol fumarate, dihydrate

Formoterol fumarate was dissolved in methanol, in an ultrasonic bath. After dissolution, water was slowly added to the solution. Several compositions of the formoterol fumarate solution were used in different experiments (Table 5).

Table 5. Compositions of the formoterol fumarat solution.

Composition no.	Solution in experiment	Concentration (w/v%)	Methanol (99.8%) (v%)	Water (v%)
3-1	3-1a	2.0	99.0	1.0
3-1	3-1b	2.0	99.0	1.0
3-2	3-2a	2.0	98.0	2.0
3-2	3-2b	2.0	98.0	2.0

The solution (several compositions) was co-introduced with the antisolvent (carbon dioxide or ethane) in the coaxial nozzle under controlled temperature and pressure (Table 6).

Table 6. SEDS processing of different solutions, using different antisolvents.

Experiments	Antisolvent	Pressure (bar)	Temperature (°C)	Flow rate antisolvent (ml/min)	Flow rate solution (ml/min)	Degradation product a (w%)
3-1a	CO_2	80	40	9.0	0.3	0.26
3-1b	ethane	80	40	9.0	0.3	0.07
3-2a	CO_2	100	45	10.0	0.3	0.22
3-2b	ethane	100	45	10.0	0.3	0.11

The particles made from a solution, using methanol and water as solvents (composition 3-1 and 3-2 in Table 5), were crystallised as formoterol fumarate dihydrate, when ethane was used as antisolvent (pXRD, TGA). The degradation products were 0.07 weight % in 3-1b and 0.11 weight % in 3-2b (HPLC).

When using carbon dioxide as antisolvent, the produced particles in experiment 3-1a contained amorphous formoterol fumarate (composition 3-1 in Table 5). Experiment 3-2a resulted in a mixture of formoterol fumarate dihydrate and formoterol fumarate anhydrate B (composition 3-2 in Table 5) (pXRD, TGA). The degradation products were 0.26 weight % in 3-1a and 0.22 weight % in 3-2a (HPLC).

The amount of degradation products are summarized in Table 6.

The experiments clearly show that by using the method of this invention, a better product is obtained with ethane as anti-solvent.

CLAIMS

1. A method of preparing drug particles by the use of a fluid gas technique process characterized by applying the fluid gas technique to an acid labile substance being in hydrate form wherein the fluid gas is selected from the group consisting of a low molecular weight, saturated or unsaturated hydrocarbon, xenon, dimethylether and a mixture of any of these gases.

2. A method according to claim 1 wherein the substance susceptible to degradation is a hydrate of omeprazole, its magnesium or sodium salt.

3. A method according to claim 1 wherein the substance susceptible to degradation is a hydrate of (S)-omeprazole, its magnesium, sodium or potassium salt.

4. A method according to claim 1 wherein the substance susceptible to degradation is a hydrate of formoterol fumarate.

5. A method according to any of the preceeding claims wherein the fluid gas is a saturated or unsaturated hydrocarbon having from 1 to 6 carbon atoms.

6. A method according to claim 6 wherein the hydrocarbon is ethane.

7. Use of a fluid gas selected from the group consisting of a low molecular weight, saturated or unsaturated hydrocarbon, xenon, dimethylether and a mixture of any of these gases in the preparation by a fluid gas technique process of drug particles which are acid labile and in hydrate form.

8. Drug particles of an acid labile substance in hydrate form which is susceptible to degradation when applied to a fluid gas technique process, which particles are obtained by a method according to any of the preceeding claims.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02152

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/14, A61K 31/41, A61K 31/44, A61K 31/165
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, PATENT ABSTRACTS OF JAPAN, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9714407 A1 (RESEARCH TRIANGLE PHARMACEUTICALS), 24 April 1997 (24.04.97), page 3, line 11 - line 19; page 4, line 7 - line 16; page 7, line 13 - line 15, see especially abstract	1,5-8
Y		2-4
	--	
Y	WO 9619198 A1 (ASTRA AKTIEBOLAG), 27 June 1996 (27.06.96), page 4, line 2 - line 6; page 5, line 17 - line 19, see especially abstract	2-4
	--	
X	WO 9003782 A2 (THE UPJOHN COMPANY), 19 April 1990 (19.04.90), page 4, line 30 - page 10, line 15	1,5-8
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2000	30 -03- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02152

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9828294 A1 (ASTRA AKTIEBOLAG), 2 July 1998 (02.07.98) -- --------	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 99/02152

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/44, 31/557

A1

(11) International Publication Number: **WO 00/35448**

(43) International Publication Date: 22 June 2000 (22.06.00)

(21) International Application Number: PCT/SE99/02315

(22) International Filing Date: 10 December 1999 (10.12.99)

(30) Priority Data:
9804314-4 14 December 1998 (14.12.98) SE

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NEW PHARMACEUTICAL FORMULATION

(57) Abstract

This invention is related to new oral pharmaceutical dosage forms comprising a proton pump inhibitor, i.e. a H^+, K^+ -ATPase inhibitor, a gastric antisecretory prostaglandin analogue compound, and optionally an additional drug such as a calcium channel blocking agent, especially for use in the treatment and prophylaxis of gastrointestinal disorders. More specifically the invention is related to new dosage forms comprising omeprazole and misoprostol. The invention is also related to a combination of the three categories of drugs, i.e. the H^+, K^+ -ATPase inhibitor, the gastric antisecretory prostaglandin analogue, and the calcium channel blocking agent. Furthermore, the invention refers to a method for the manufacture of the described dosage forms and their use in medicine, as well as blister packs comprising these medicaments.

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NEW PHARMACEUTICAL FORMULATION

Field of the invention

This invention is related to new oral pharmaceutical dosage forms comprising a H^+, K^+-ATPase inhibitor, a gastric antisecretory prostaglandin analogue compound, and optionally an additional drug such as a calcium channel blocking agent, especially for use in the treatment and prophylaxis of gastrointestinal disorders. More specifically the invention is related to new dosage forms comprising omeprazole and misoprostol. The invention is also related to a combination of the three categories of drugs, i.e. the H^+, K^+-ATPase inhibitor, the gastric antisecretory prostaglandin analogue and the calcium channel blocking agent. Furthermore, the invention refers to a method for the manufacture of the described dosage forms and their use in medicine, as well as blisterpacks comprising these medicaments.

Background of the invention and prior art

H^+, K^+-ATPase inhibitors, such as the the proton pump inhibitors known under the generic names omeprazole, lansoprazole, pantoprazole, rabeprazole and leminoprazole are for instance described in EP 5129, EP 174 726, EP 166 287, GB 2 163 747 and WO 90/06925. The expression H^+, K^+-ATPase inhibitors and proton pump inhibitors are interchangable with each other within the context of the present application. Proton pump inhibitors are generally known to be useful for inhibiting gastric acid secretion in mammals and man by controlling gastric acid secretion in the final step of the secretory pathway. They heal gastric as well as duodenal ulcers in patients on continuous treatment with Non-steroidal anti-inflammatory drugs (NSAID) as in non-NSAID users. WO 96/01735 describes new fixed dosage forms comprising a proton pump inhibitor and an NSAID and their use in the treatment or prevention of gastrointestinal side-effects associated with NSAID treatment.

Prostaglandin analogue compounds, such as the ones known under the generic names misoprostol, enoprostil, enisoprost, rosaprostol and miraprostal are orally active PGE_1 -

analogues with mucosal protective and antisecretory properties, and these type of compounds are for instance described in US 3,965,143 and US 4,178,457. They are mainly used for prevention of gastric and duodenal ulcers associated with NSAID treatment. Usually they are administered in separate, single unit dosage form, and sometimes in combination with an NSAID in a fixed dosage form.

For gastric antisecretory prostaglandin analogues there are adverse drug reactions reported. The use of misoprostol for instance, may cause diarrhoea, abdominal pain and other adverse effects connected to the gastrointestinal system. Dosage regimen for misoprostol includes frequently intake of a dosage form, sometimes up to 4 times a day. This frequent intake, in addition to the undesired gastrointestinal side-effects with gastric antisecretory prostaglandin analogues implicates problems with compliance. On the other hand, the proton pump inhibitor, omeprazole, has only few dosage related adverse effects.

A combination of two or more active agents achieving similar physiological effect, but working through different mechanisms, usually gives a possibility to reduce the doses of each single drug and still achieve the desired effect. This will reduce the risk for dose dependent adverse side-effects. Furthermore, if one of the drugs fails due to individual patient response, the other component of the treatment regimen may be successful.

These factors implicates advantages of combining two or more antiulcerative drug in general, and to combine misoprostol with other antiulcerative drugs in particular. Administration of two or even more different dosage forms to the patient is not convenient or satisfactory for achieving the most optimal result. As patient compliance is a major factor in receiving a good medical result, it would be advantageous to combine the different drugs into one single pharmaceutical dosage unit, which reduces the number of pills for the patient at each dosing occasion. If one or more of the drugs can be provided in dosage forms with extended release the efficacy may be further enhanced.

Previously suggested combination therapies comprising antiulcerative agents are for instance combinations of a histamine H_2- receptor antagonist, such as cimetidine or ranitidine, and sucralfate. Other proposed therapies are for instance a combination of omeprazole and sucralfate, a combination of ranitidine and cimetidine, or a combination of ranitidine and misoprostol. See for instance Van Deventer GM et al., Am J Med 1985; 79: 39 - 44, and Houston LJ et al, Am J Gastroenterol 1993; 88: 675 - 679.

A combination therapy of misoprostol and a calcium channel blocking agent, such as verapamil, has been proposed and tested with respect to mucosal-protective effects in rats by reducing leukotriene synthesis and increasing prostaglandin synthesis. See Fedorak, R.N. et al, Gastroenterology 1992;102: 1229-35.

To combine the proton pump inhibitor omeprazole and the gastric antisecretory prostaglandin analogue enprostil for the treatment of gastrointestinal disorders is known from Tari, A. et al, Digestive Diseases and Sciences, 1997; 42: 1741-1746 and from Meijer, J.L. et al, Digestive Diseases and Sciences, 1994; 39: 609-616.

However, a fixed unit dosage form comprising a H^+, K^+-ATPase inhibitor in combination with a gastric antisecretory prostaglandin analogue has so far not been suggested.

Furthermore, there is no suggestion or description in the prior art of a combination comprising a H^+, K^+-ATPase inhibitor, a gastric antisecretory prostaglandin analogue and a calcium channel blocking agent. Neither is the Applicant aware of any oral pharmaceutical dosage forms comprising such a combination, especially not in the form of a blister pack or a fixed unit dosage form.

Summary of the invention

One aspect of the present invention is to provide a fixed unit dosage form for oral administration comprising a H^+, K^+-ATPase inhibitor and a gastric antisecretory prostaglandin analogue.

A further aspect of the invention is to provide dosage forms of a H^+, K^+-ATPase inhibitor and a gastric antisecretory prostaglandin analogue, wherein the latter is in a form which provides extended release, such a dosage form reduces dosing frequency and dose related adverse side-effects.

An additional aspect of the invention is to provide a combination therapy of a H^+, K^+-ATPase inhibitor, a gastric antisecretory prostaglandin analogue, and a component which potentiates the effect of the prostaglandin analogue, e.g. a calcium channel blocking agent. The combination may be provided in the form of fixed unit dosage forms.

Detailed description of the invention

According to the present invention, a fixed dosage form comprising a H^+, K^+-ATPase inhibitor, a gastric antisecretory prostaglandin analogue compound, and optionally a calcium channel blocking agent, may principally be constructed in the form of a two-layer tablet, or a tablet core layered with a coating layer, or a press-coated tablet, wherein the different drugs are situated in different parts of the tablet. Alternatively, the dosage form may be a tablet or a capsule comprising either two or three populations of units each one containing one of the drugs, or a population of multiple layered units comprising a combination of the different drugs, or they may be constructed as a capsule containing one or two of the drugs as a population of units and the other drug as a single unit also positioned within the same capsule.

Preferred types of dosage forms according to the invention are described more in detail below under separate headings, and in the following examples.

Two-layer tablet

One layer comprises the proton puimp inhibitor as a multitude of enteric coated pellets dispersed in pharmaceutically acceptable excipients. These pellets may have the characteristics of immediate release, delayed pulsed release, delayed dual pulsed release, delayed multiple pulsed release or extended release, or any combination thereof. If the proton pump inhibitor is to be constructed as an extended release part layer, it may be designed in the form of a hydrophilic matrix layer comprising the proton pump inhibitor. In this latter situation appropriate measures for protecting the proton pump inhibitor from contact with acidic fluids has to be taken.

The other layer comprises a gastric antisecretory prostaglandin analogue, and optionally a calcium channel blocking agent. This layer may be formulated to provide immediate or extended release of the drug(s). The extended release characteristics may be achieved by using membrane coated extended release pellets dispersed in pharmaceutically acceptable excipients or by dispersing the drug in a hydrophilic or hydrophobic matrix with extended release properties. Immediate release characteristics may be achieved by using a conventional tablet granulation procedure, or by incorporating the prostaglandin analogue in fast dissolving pellets, which are dispersed in pharmaceutically acceptable excipients. It is also possible in a first layer to include the proton pump inhibitor pellets together with the pellets comprising the prostaglandin analogue, and optionally in a second layer include a calcium channel blocking agent.

Tablet core comprising one drug layered with a second drug

Each tablet comprises a tablet core containing a proton pump inhibitor which tablet core is spray coated with a layer comprising a gastric antisecretory prostaglandin analogue. The tablet cores may be prepared as described below under the heading " *Press-coated/coated tablets*". The prepared tablets which are enteric coated are further layered with a suspension comprising the prostaglandin analogue. Alternatively, the tablet cores are layered in the same way as described below for pellets preparation. However, a prepared

tablet core has a larger size than cores intended for pellets preparation, i.e. preferably the tablet core has a size of 3 - 12 mm in diameter.

Press-coated/ coated tablets

An inner tablet core is prepared by tableting technique according to known art. The tablet core comprises one of the active ingredients, preferably a proton pump inhibitor, optionally in combination with a calcium channel blocking agent. This tablet core is then coated with an enteric coating layer, and optionally a separating layer has been applied before the enteric coating layer. The enteric coating layer protects the acidic susceptible proton pump inhibitor from gastric acid, i.e. it is a layer not dissolving in gastric acid environment but dissolving or disintegrating in the small intestines. A further coating layer comprising the second active ingredient, optionally in combination with a calcium channel blocking agent, is applied on the enteric coating layer by compression. Either the tablet core or the outer layer may give the characteristics of an extended or immediate release preparation.

Tablet or capsule comprising a multitude of drug-containing units

Such dosage forms my be divided into two principally different categories; e.g. (i) one-population of multiple layered units, and (ii) two-populations of units.

(i) One-population of multiple layered units intended for tablet or capsule formulations.

The first category comprising one population of equally constructed units or pellets, optionally dispersed in a pharmaceutically acceptable tablet excipient.

Each unit comprises a proton pump inhibitor and a gastric antisecretory prostaglandin analogue as the pharmaceutically active agents. The units contain multiple layers and the different active substances are situated in different layers. The proton pump layer is positioned on the inside of an enteric coating layer, optionally a separating layer may be positioned in between the proton pump layer and the enteric coating layer. The layer comprising a gastric antisecretory prostaglandin analogue, and optionally a calcium

channel blocking agent, is positioned exterior to the proton pump layer, but it may be positioned interior or exterior with regard to the enteric coating layer.

The proton pump inhibitor comprising layer may have characteristics of immediate release or extended release, which also is applicable for the layer comprising the gastric antisecretory prostaglandin analogue, though extended release is preferred. The prepared drug containing units may be filled in capsules or mixed with pharmaceutically acceptable tablet excipients and compressed to multiple unit tablets.

(ii) Two-populations of units intended for tablet or capsule formulations.
The second category comprises a mixture of two different populations of within each population equally constructed units or pellets, optionally dispersed in a pharmaceutically acceptable tablet excipients. One population comprises a proton pump inhibitor, and the other population comprises a gastric antisecretory prostaglandin analogue as the pharmaceutically active agent. Optionally, a third population of units comprising a calcium blocking agent is included in the mixture.

These formulations are based on the mixing of a population of units comprising a gastric antisecretory prostaglandin analogue with a population of units comprising a proton pump inhibitor. The mixture is filled in capsules, or further mixed with pharmaceutically acceptable tablet excipients and compressed to a tablet. The tablet excipients may be previously granulated or just admixed to the layered units before the compression to tablets.

Units comprising a gastric antisecretory prostaglandin analogue.
These units may be prepared by prilling, extrusion and spheronization, congealing, direct pelletization in a mixer, melt granulation with suitable polymeric additives, by incorporation in porous carriers, or by layering on a starting seed, or any other suitable techniques known in the art. The units may be formulated with immediate or extended

release characteristics. If suitable, an additional coating layer providing extended release may be applied onto the units.

To increase the residence time in the stomach for the units comprising a gastric antisecretory prostaglandin analogue, the gastric antisecretory prostaglandin analogue is included in a hydrophilic matrix together with a suitable concentration of a sodium hydrogen carbonate and formulated to pellets. When the pellets come in contact with the acidic gastric environment they develop small bubbles of carbon dioxide making the density of these pellets to decrease, and the pellets to flow in the stomach.

Units having immediate release characteristics may be prepared by incorporating the active substance in porous amorphous silica particles or by layering the active substance on sugar seeds.

Units comprising a proton pump inhibitor.
These units may be prepared for either immediate release, extended release or delayed pulsed release of the proton pump inhibitor. WO 97/ 02020 describes pellets of pantoprazole coated with extended release membrane which technology is suitable also for other extended release units. Units suitable for immediate release of the proton pump inhibitor are described in EP 502 556 and units especially designed for use in tableted dosage form are described in WO 96/ 01624, hereby incorporated by references.

Capsule comprising two or more drugs in a single unit in combination with multiple units.
The capsule comprises one drug in a single unit, i.e. a tablet, and one or two drugs in the form of two populations of units, or one population of units and one or two single tablets.

Units suitable for a capsule formulation may be prepared as described above, i.e. (i) one-population of multiple layered units comprising a proton pump inhibitor and a gastric antisecretory prostaglandin analogue, or (ii) two-populations of units. The capsule may

comprise two or three different drugs, i.e. a third population of units comprising a calcium channel blocking agent may be included.

The single unit may comprise any of the drugs, i.e. the proton pump inhibitor, the gastric antisecretory prostaglandin analogue, or optionally the calcium channel blocking agent. When the single unit comprises the prostaglandin analogue, it may have immediate or extended release characteristics. Immediate release single units are preferably constructed according to principles known in the art. Extended release single units are preferably constructed as hydrophilic matrix units, or as hydrophobic matrix units, or as membrane coated units.

Techniques for application of layers.

The layer can be applied by coating or layering procedures in suitable equipments such as a coating pan, a coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the layer(s) may be applied by using powder coating or press-coating techniques.

Excipients.

Different pharmaceutically acceptable excipients may be used in combination with the active substances in the claimed dosage forms. Such excipients are for instance binding agents, fillers, pH-buffering substances, pigments and the like.

Separating layer(s).

Suitable materials for the separating layer are pharmaceutically acceptable compounds such as, for instance, sugar, or filmforming compounds as polyethylene glycol, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc, pH-buffering substances and other additives may also be

included into the separating layer. The separating layer is composed in such a way that it has properties to be water soluble or disintegrating in water.

Enteric coating layer(s).

The enteric coating layer material may be dispersed or dissolved in water or dissolved in suitable organic solvents. As enteric coating layer polymers one or more, separately or dissolved in combination, of the following can be used, but are not restricted to; e.g. methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethylcellulose, shellac or other suitable enteric coating layer polymer(s) known in the art.

Additives such as dispersants, colorants, pigments, additional polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the separating layer and/or the enteric coating layer or in an additional tablet coat as described below. Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible core material. The enteric coating layer(s) constitutes a thickness of approximately at least 10 μm, preferably more than 20 μm. The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

The enteric coating layers may also contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, glycerol monoesters, polysorbates or other plasticizers and mixtures thereof. The amount of plasticizer is preferably optimized for each formula, in relation to the selected polymer(s), selected plasticizer(s) and the applied amount of said polymer(s).

Over-coating layer.

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan,

coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer(s). The maximum thickness of the applied over-coating layer(s) is normally only limited by processing conditions.

Hydrophilic matrix.

The active substance, i.e. the drug, is embedded in a hydrophilic polymer optionally together with pharmaceutically acceptable excipients. Suitable hydrophilic polymers are for instance hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethylhydroxy ethylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, poloxamer, polyethylene oxides, polyvinylpyrrolidone, polyvinyl alcohols, tragacanth, xanthan and guar gums or any other suitable hydrophilic polymer(s). These polymers can be used alone or in mixtures with each other.

The amount of hydrophilic polymer in the matrix is preferably 15 - 85 % w/w (calculated on the unit weight) of a hydrophilic polymer(s) chosen among the above mentioned. Especially preferred polymers in the hydrophilic matrix unit are hydroxypropyl methylcellulose or polyethylene oxides.

Excipients preferred in the matrix are fillers which will result in technically good tableting properties, i. e. sodium aluminium silicate, mannitol or calcium phosphate (Emcompress™). A preferred matrix comprises 15 - 85 % w/w (calculated on the unit weight) of a hydrophilic polymer chosen as above, and 80 - 10 % w/w (calculated on the unit weight) of sodium aluminium silicate or calcium phosphate (Emcompress™).

Hydrophobic matrix.

The active substance, i.e. the drug, is embedded in a hydrophobic matrix optionally together with pharmaceutically acceptable excipients. The hydrophobic matrix comprises a hydrophobizing agent and/or a hydrophobic polymer. Suitable material for the hydrophobic matrix are for instance a hydrophobizing agents such as cetanol, cetostearyl alcohol, cetyl palmitate, waxes like carnauba wax, paraffin, magnesium stearate, sodium stearyl fumarate, and medium- or long- chain glycerol esters alone or in any mixtures. Hydrophobic polymers are exemplified by for instance polyvinyl chloride, ethyl cellulose, polyvinyl acetate and acrylic acid copolymers, such as Eudragith™ RS and RL. The polymers may be used alone or as mixtures. Furthermore, the polymers may be combined with the hydrophobizing agent.

As binders for the hydrophobic matrix may be used either hydrophilic or hydrophobic polymers.

It is important that the matrix comprises at least one component that is soluble in aqueous media such as the intestinal fluids. This component dissolves and leaves a porous network open for passage of dissolving fluids and dissolved drug. This soluble component may for instance be a sugar. It is preferred that the matrix comprises 10 - 70 % w/w (calculated on the unit weight) of a hydrophobizing agent or a hydrophobic polymer and 10-70% w/w of a water soluble component, both described above, or any combinations thereof.

Another preferred matrix comprises as an additive a slightly soluble or less soluble component. As such components may any of the following be added: sodium aluminium silicate, calcium phosphate, aerosil, titanium dioxide, magnesium carbonates, or other neutral or alkaline compounds that are slightly soluble or less soluble, herein with regard to solubility in water. Slightly soluble is defined in compliance with the European Pharmacopea (Edition 3) under the heading "General notices". Such a matrix comprises preferably 10 - 70 % w/w (calculated on the unit weight) of a hydrophobizing agent or a

hydrophobic polymer or any combinations thereof, together with preferably 10 - 70 % w/w of a slightly soluble or less soluble component. As such a component is especially preferred sodium aluminium silicate.

The final dissolution profile may sometimes be adjusted by thermal treatment of the hydrophobic matrix unit for a short period, to achieve temperatures at or above the softening temperature of the hydrophobizing agents.

Particles comprising oily material, such as for instance misoprostol.

One way of preparing a free-flowing particle of oily/greasy/sticky material is to incorporate it into inorganic porous particle material, such as for instance ceramic hydroxy apatite or amorphous silica. The ceramic hydroxy apatite has preferably a range particle diameter size between 5 - 250 μm, more preferably 80 - 150 μm, a nominal pore diameter between 50 - 1 000 Å, more preferably 500 - 1 000 Å; and a surface area between 40 - 50 m^2 /g. The amorphous silica has preferably a median pore diameter between 50 - 1 000 Å, more preferably 50 - 200 Å; a pore volume of 0.8 - 1.2 ml/g; and a surface area between 500 - 600 m^2/g.

The incorporation of the oily material may be accomplished by known conventional methods, such as dissolve the oil in a suitable solvent and then add the porous particle material and dry the mixture. Alternatively, the oil may be mixed directly with the porous particle material, or the incorporation may be done using phase separation from solution containing particles accomplished by the addition of a non-solvent. The loaded porous particles can be filled into capsules or compressed to tablets.

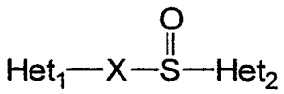
Preparation of particles comprising oily material in small amount may also be accomplished by conventional methods, such as layering or coating on inert seeds or by extrusion/ spheronization.

Tablet coat

Prepared tablets are optionally covered with film forming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a tablet coat comprising a polymeric material may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance. The tablet coat may especially comprise a pigment to protect light sensitive components of the dosage form.

Active ingredients.

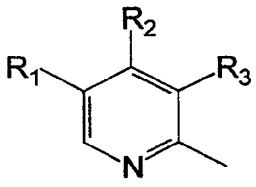
I) H^+, K^+-ATPase inhibitors, i.e. proton pump inhibitors suitable for the claimed therapies and the pharmaceutical formulations according to the present invention are compounds of the general formula I, an alkaline salt thereof, one of the single enantiomers thereof or an alkaline salt of one of the enantiomers



I

wherein

Het_1 is



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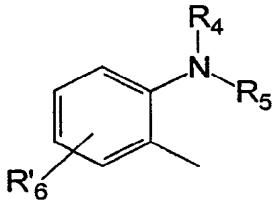
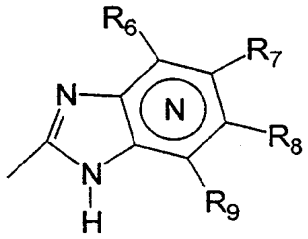


Het_2 is



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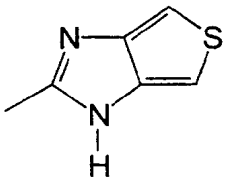
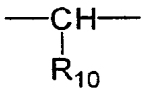


X =



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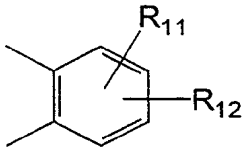


wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and arylalkyl;

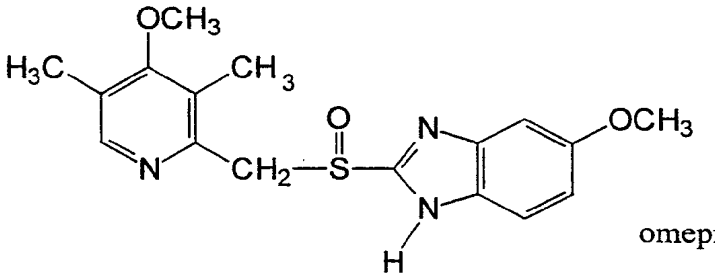
R_6' is hydrogen, halogen, trifluoromethyl, alkyl or alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolinyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

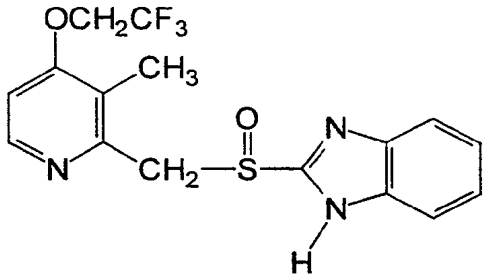
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl.

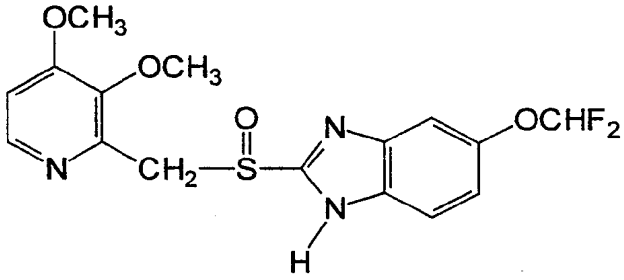
Examples of specifically interesting compounds according to formula I are



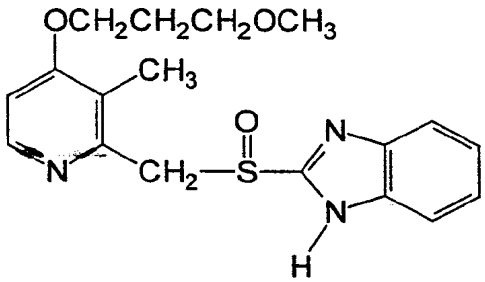
omeprazole



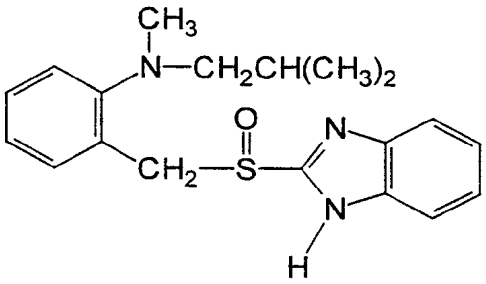
lansoprazole



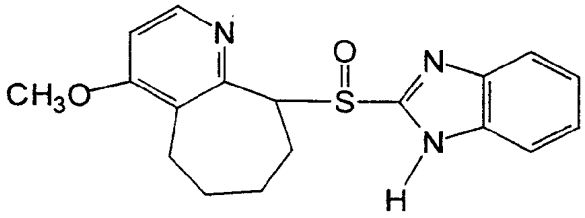
pantoprazole

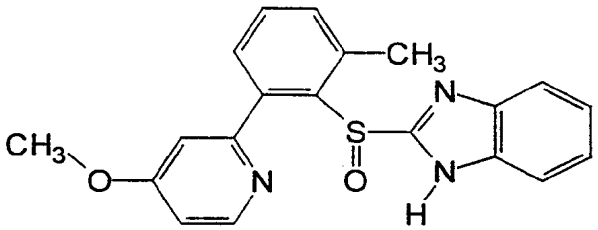


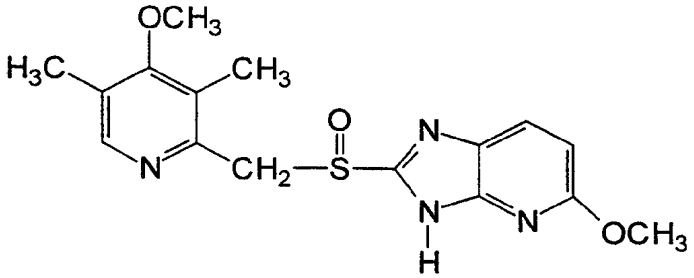
pariprazole

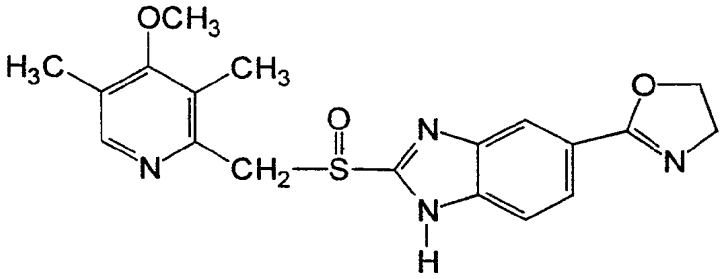


leminoprazole







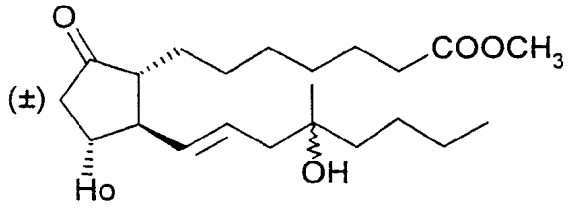


The compound suitable for the formulations according to the present invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+}, Ca^{2+}, Na^{+} or K^{+} salts, preferably the Mg^{2+} salts. The compounds may also be used in the form of one of its single enantiomers or an alkaline salt of the single enantiomer.

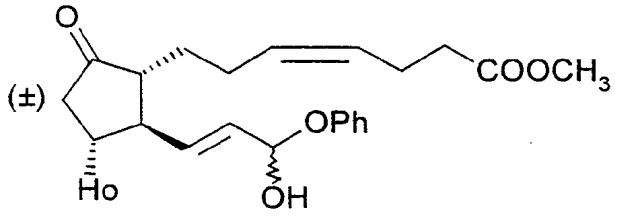
Preferred compounds for the oral pharmaceutical preparations according to the present invention are omeprazole, a magnesium salt of omeprazole or a magnesium salt of the (-)-enantiomer of omeprazole. Omeprazole and related substances as well as their preparations are described in EP 5129, EP 124 495, WO 95/01977, WO 94/27988 hereby incorporated in a whole by references.

The above compounds are susceptible to degradation/transformation in acidic and neutral media. Generally, the degradation is catalyzed by acidic reacting compounds and the active compounds are stabilized with alkaline reacting compounds. There are different enteric coating layered preparations comprising omeprazole as well as other proton pump inhibitors described in the prior art, see for instance US-A 4,853,230, WO 95/ 01783 and WO 96/ 01624. Especially, the latter describes alternative manufacturing methods for the preparation of enteric coating layered pellets comprising omeprazole and similar compounds. These patents are hereby incorporated in whole by references.

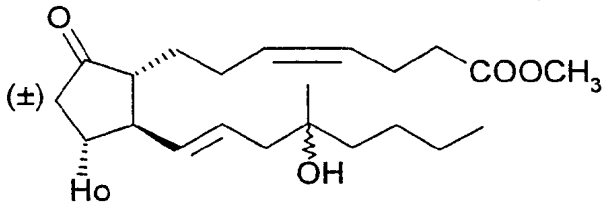
II) Gastric anti-secretory prostaglandin analogues suitable for the claimed therapies and formulations are for instance misoprostol, enprostil, enisoprost, rosaprostol, miraprostal and analogues with the following formulas



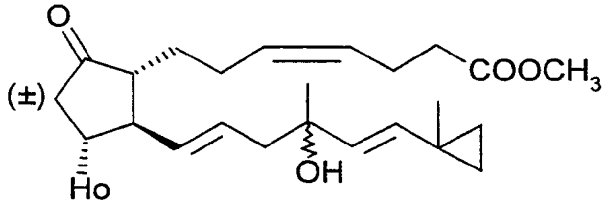
misoprostol

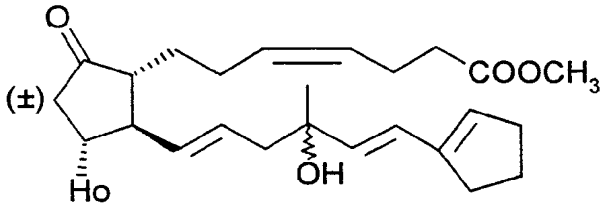


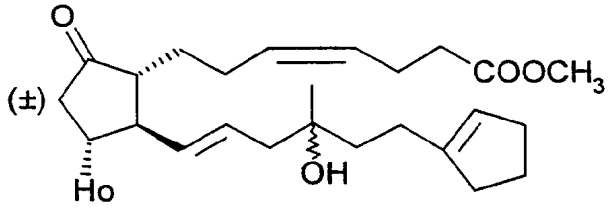
enprostil

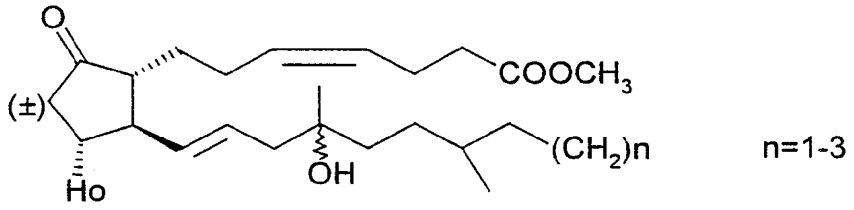


enisoprost









The above compounds may be used in the form of their single enantiomers.

III) Calcium channel blockers which optionally may be used in combination with a proton pump inhibitor and a gastric antisecretory prostaglandin analogue are for instance the following ones known under the generic names verapamil, felodipin, nifedipin and nisoldipine.

Use of the preparations

The dosage forms according to the present invention, are suitable for oral administration. The dose will depend on the nature and severity of the disease to be treated. The dose may also vary according to the age, body weight, and response of the individual patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. In the treatment of other conditions higher doses than average will be used. The dosage forms may also be used in combinations with other dosage forms comprising for instance a calcium channel blocking agent, an NSAID, or other antiulcerative agents.

The dosage forms according to the invention are especially advantageous for patients experiencing gastrointestinal side-effects caused by gastric antisecretory prostaglandin analogues, when used alone. The new dosage forms are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the

mode of administration and disease. In general each dosage form will comprise 1-200 mg of the H^+, K^+-ATPase inhibitor and 80 - 1 000 μg of the gastric antisecretory prostaglandin analogue(-s). Preferably, each dosage form will comprise 5-80 mg of the H^+, K^+-ATPase inhibitor and 100 - 800 μg of the gastric antisecretory prostaglandin analogue(-s), and more preferably 10-40 mg of the H^+, K^+-ATPase inhibitor and 150 - 600 μg of the gastric antisecretory prostaglandin analogue(-s), respectively. Especially preferred combinations comprise omeprazole and misoprotol in a range of 15: 1 to 400: 1, for instance 20 mg omeprazole together with 200 μg misoprostol, or 20 mg omeprazole and 400 μg misoprostol. In the latter one, misoprostol is preferably present in the form of an extended release formulation.

The optional calcium channel blocking agent may be present in an amount of 1 - 100 mg.

The multiple unit preparation, i.e. a capsule or a tableted dosage form, may also be suitable for dispersion in an aqueous liquid with slightly acidic pH-value. The dispension should be prepared just before being orally administered or fed through a naso-gastric tube.

The present invention is illustrated more by detail in the following non-limiting examples.

Examples

Example 1.

Two-layer tablet comprising misoprostol and omeprazole (magnesium salt).

Principle: one layer comprises 400 μg misoprostol in a hydrophilic matrix, and the other layer comprises 20 mg omeprazole (magnesium salt) in the form of enteric coated pellets mixed with tableting excipients.

Extended release granules comprising misoprostol were prepared according to this recipe;

Misoprostol	0.4 parts by weight
Ethanol 95% (w/v)	410 parts by weight
Hydroxypropyl methyl cellulose 50 cps	400 parts by weight
Sodium stearyl fumarate	4 parts by weight

The misoprostol was dissolved in half the amount of ethanol. This solution was poured on the HPMC powder during mixing. The rest of the ethanol was added to achieve a suitable consistence of the mass. The mass was dried under mild conditions, and the particle size of the dried granules was reduced until all granules passed a 0.8 mm sieve. 1% (w/w) of sodium stearyl fumarate was admixed.

Enteric coated pellets comprising omeprazole magnesium salt was prepared according to the following recipe;

Core material

Magnesium omeprazole	12.00 kg
Sugar spheres (non-pareil™)	12.00 kg
Hydroxypropyl methylcellulose	1.8 kg
Water purified	35.4 kg

Separating layer

Core material (acc. to above)	23.50 kg
Hydroxypropyl cellulose	2.35 kg
Talc	4.03 kg
Magnesium Stearate	0.34 kg
Water purified	48.00 kg

Enteric coating

Coated pellets (acc. to above)	29.00 kg
Methacrylic acid copolymer (30% suspension)	38.70 kg
Triethyl citrate	3.48 kg

Mono- and diglycerides (NF)	0.58 kg
Polysorbate 80	0.06 kg
Water purified	22.68 kg

Over-coating

Enteric coated pellets	44.7 kg
Hydroxypropyl methylcellulose	0.58 kg
Mg-Stearate	0.017 kg
Water purified	11.6 kg

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto non-pareil from a water suspension containing the dissolved binder and magnesium omeprazole.

The prepared core material was coated in a fluid bed apparatus with the separating layer material. The enteric coating was sprayed onto the coated pellets in a fluid bed apparatus. In the same type of apparatus the enteric coated pellets were coated with an over-coat. The over-coated pellets were classified by sieving.

Tableting excipient for mixing with enteric coated pellets was prepared by mixing the following ingredients to homogeneity;

Tableting excipient;

Microcrystalline cellulose special coarse grade PH 102		12.12 g
Microcrystalline cellulose PH 101		6.06 g
Polyvinyl pyrrolidone cross-linked		1.82 g
	Sum:	20.00 g

Tablets were compressed on a tablet machine equipped with 9x17 mm oval punches (giving elliptically shaped tablets), by pre-compressing 404 mg of the misoprostol-containing granules and then filling a mixture consisting of 100 mg omeprazole pellets (according to above) and 200 mg of the tableting excipient mix, and compressing. A two

layered tablet was obtained with an acid resistance of 91% (mean value of 4 tablets). The release of omeprazole at pH 6.8 from a tablet pre-exposed 2 h in 0.1 M HCl, spectrophotometric determination, was 89% within 30 min.

Example 2.

Enteric coated pellets comprising magnesium salt of S-omeprazole, layered with misoprostol.

Principle: enteric coated pellets comprising approx. 225 mg/g magnesium salt of S-omeprazole layered with an outer fast dissolving layer comprising approx. 3.6 mg/g misoprostol.

Enteric coated pellets comprising magnesium salt of S-omeprazole were prepared according to the following recipe;

Core material	
S-omeprazole Mg-salt	20.0 kg
Non-pareil™	25.0 kg
Hydroxypropyl methylcellulose (HPMC)	3.0 kg
Polysorbate 80	0.4 kg
Water purified	93.6 kg
Separating layer	
Core material (acc. to above)	50.0 kg
Hydroxypropyl cellulose	5.5 kg
Talc	20.5 kg
Magnesium Stearate	1.4 kg
Water purified	193.8 kg

Enteric coating

Coated pellets (acc. to above)	30.0 kg
Methacrylic acid copolymer (30% suspension)	30.0 kg
Triethyl citrate	0.9 kg
Mono- and diglycerides (NF)	0.5 kg
Polysorbate 80	0.05 kg
Water purified	12.9 kg

Suspension layering was performed in a fluid bed apparatus. S-omeprazole magnesium salt was sprayed onto non-pareil from a water suspension containing the dissolved binder. The prepared core material was coated in a fluid bed apparatus with the separating layer material. The enteric coating was sprayed onto the coated pellets in a fluid bed apparatus. The enteric coated pellets were classified by sieving.

The enteric coated pellets were further coated with a solution of HPMC and misoprostol in a fluid bed apparatus, using the following composition;

Enteric coated pellets (according to above)	100	g
Solution;		
EtOH 95% (w/v)	125	g
Misoprostol	0.46	g
Water, purified	125	g
Hydroxypropyl methyl cellulose (HPMC) 6 cps	5.3	g
Colloidal silica (Aerosil™)	0.5	g

First the misoprostol was dissolved in the ethanol and then the water was added. The HPMC was admixed and dissolved. Finally the Aerosil™ was dispersed in the solution. The obtained pellets were classified by sieving. The acid resistance of the prepared pellets was 99.6%. The prepared pellets may be mixed with tablet excipients and compressed into

a multiple unit tablet as described in Example 5, or filled into a capsule suitable for the desired dose.

Example 3.

Two-layer tablet with 400 µg misoprostol and 10 mg of felodipine comprised in a hydrophilic matrix as one layer, and the other layer comprising 20 mg omeprazole (magnesium salt) in the form of enteric coated pellets mixed with tableting excipients.

Extended release granules comprising misoprostol and felodine are prepared according to the following recipe;

	parts by weight
Misoprostol	0.4
Felodipine	10
Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)	10
Ethanol 95% (w/v)	400
Hydroxypropyl methyl cellulose 50 cps	400
Sodium stearyl fumarate	4

The misoprostol is dissolved in half the amount of ethanol. Another solution is made by dissolving 10 parts of the felodipine and 10 parts of the Cremophor RH 40 in 60 parts of ethanol. These solutions are poured on the HPMC powder during mixing. Additionally ethanol (approximately 140 parts) may be added to get satisfactory consistency of the mass. The mass is dried on a tray (under mild conditions). The particle size of the dried granules is reduced until all granules passed a 0.8 mm sieve. Thereafter 1% (w/w) of sodium stearyl fumarate is admixed.

Enteric coated pellets comprising omeprazole magnesium salt was prepared and mixed with tabletting excipients according to Example 1. Two-layer tablets containing

misoprostol 400 µg, felodipin 10 mg, and omeprazole 20 mg were prepared as described in Example 1.

The tablets are coated with a solution of HPMC and PEG having pigments dispersed therein, in a suitable coating apparatus, e.g. rotating drum coater, using the following composition;

Tablets (according to above)	724	parts by weight
Solution;		
Water purified	122	parts by weight
Hydroxypropyl methyl cellulose (HPMC) 6 cps	14	parts by weight
Polyethylene glycol (PEG) 6000	4	parts by weight
Titanium dioxide	2	parts by weight
Iron oxide yellow	2	parts by weight

The coating is continued until average tablet weight has increased with 14 - 20 mg.

Example 4.

Capsule formulation comprising pantoprazole and misoprostol pellets. (40 mg pantoprazole and 200 µg misoprostol).

Pantoprazole enteric coated pellets is prepared according to the following recipe;

<u>Core material</u>	
Pantoprazole	100 g
Non-pareil™	200 g
Hydroxypropylcellulose LF	25 g
Water purified	607 g

Separating layer	
Core material (acc. to above)	200 g
Hydroxypropyl cellulose LF	20 g
Talc	34.3 g
Magnesium Stearate	2.9 g
Water purified	400 g

Enteric coating	
Coated pellets (acc. to above)	200 g
Methacrylic acid copolymer, 30% suspension	333 g
Triethyl citrate	30 g
Mono- and diglycerides (NF)	5 g
Polysorbate 80	0.5 g
Water purified	281.5 g

Suspension layering is performed in a fluid bed apparatus. Pantoprazole is sprayed onto non-pareil from a water suspension containing the dissolved binder.
The prepared core material is coated in a fluid bed apparatus with the separating layer material. The enteric coating is sprayed onto the coated pellets in a fluid bed apparatus. The pellets are classified by sieving.

Misoprostol pellets are prepared by coating inert sugar spheres in a fluid bed according to the following recipe;

Sugar spheres (Non Pareil™)	100	g
Solution;		
EtOH 95% (w/v)	125	g
Misoprostol	0.46	g
Water, purified	125	g

Hydroxypropyl methyl cellulose (HPMC) 6 cps	5.34 g
Colloidal silica (Aerosil™)	0.50 g

First the misoprostol is dissolved in the ethanol and then the water is added. The HPMC is admixed and dissolved. Finally the Aerosil™ is dispersed in the solution. The obtained pellets are classified by sieving.

Capsule filling;

266 mg enteric coated pantoprazole pellets and pellets corresponding to 200 μg of misoprostol (i.e. approx. 55 mg) are filled into a No. 1 hard gelatin capsule.

Example 5.

Multiple unit tablet comprising lansoprazole and misoprostol pellets. (60 mg lansoprazole and 200 μg of misoprostol).

Lansoprazole pellets are prepared according to the following recipe;

Core material

Lansoprazole	370 g
Non-pareil™	400 g
Hydroxypropyl methylcellulose	76 g
Sodium laurylsulphate	2.8 g
Water purified	1360 g

Separating layer

Core material (acc. to above)	400 g
Hydroxypropyl cellulose	40 g
Talc	68.6 g
Magnesium Stearate	5.7 g
Water purified	800 g

Enteric coating	
Coated pellets (acc. to above)	400 g
Methacrylic acid copolymer 30% suspension	667 g
(containing dry materials	200 g)
Triethyl citrate	60 g
Mono- and diglycerides (NF)	10 g
Polysorbate 80	1 g
Water purified	420 g

Over-coating	
Enteric coated pellets	500 g
Hydroxypropyl methylcellulose	6.5 g
Mg-Stearate	0.2 g
Water purified	130 g

The enteric coated pellets comprising lansoprazole are prepared as described in Example 1, with lansoprazole replacing omeprazole.

Tablets	mg/tablet
Pellets comprising lansoprazole (according to above)	approx. 285
Pellets comprising misoprostol (according to Ex . 4)	approx. 55
Microcrystalline cellulose PH 102	205
Microcrystalline cellulose PH 101	205
Polyvinyl pyrrolidone cross-linked	30
Sodium stearyl fumarate	4

First the microcrystalline celluloses and polyvinyl pyrrolidone are mixed to homogeneity. Then the lubricant sodium stearyl fumarate is admixed, and thereafter the lansoprazole comprising pellets and the misoprostol comprising pellets are added, and mixed until homogeneity.

Compression to tablets is done by compressing the mixture on a tablet machine equipped with 9x21 mm oval punches.

Example 6.

Two-layer tablet with 200 µg misoprostol in one layer, and the other layer comprises 10 mg S-omeprazole (magnesium salt) containing delayed pulsed release pellets mixed with tableting excipients.

Granules comprising misoprostol are prepared according to this recipe;

	parts by weight
Misoprostol	0.2
Ethanol 95% (w/v)	300
Water purified	110
Hydroxypropyl methyl cellulose 6 cps	50
Microcrystalline cellulose PH 101	350
Sodium stearyl fumarate	4

The misoprostol is dissolved in 200 parts of ethanol. This solution is poured on the HPMC and microcrystalline cellulose powders during mixing. Then a satisfactory amount of a mixture consisting of 100 parts of ethanol and 110 parts of water is admixed until satisfactory consistency of the mass is obtained. The mass is dried under mild conditions. The particle size of the dried granules is reduced until all granules pass a 0.8 mm sieve. Thereafter 1% (w/w) of sodium stearyl fumarate is admixed.

Preparation of delayed pulsed release pellets comprising magnesium salt of S-omeprazole (pellet strength approx. 44 mg/g).

Preparation of core material (spheres layered with drug).

A drug containing suspension is made according to the composition below;

S-omeprazole Mg-salt	100g
HPMC, 6cps	15 g
Polysorbate 80	2 g
Purified water	323 g

HPMC is dissolved in water during stirring with subsequent addition of Polysobate 80 and the drug. The suspension is sprayed onto 290 g of sugar spheres (Non-pareil) in a fluidized bed. The product weight is approx. 395 g.

Application of swelling layer

A (water free) suspension containing in water highly swellable substances is prepared according to the following composition;

Low-substituted hydroxypropylcellulose (L-HPC)	162 g
Hydroxypropylcellulose LF (HPC-LF)	74 g
Talc	354 g
EtOH (99.5%)	3100 g

HPC-LF is dissolved in ethanol during stirring, then the talc and the swelling agent L-HPC are added. The suspension is sprayed onto 175 g drug containing pellets from above in a Wurster equipped fluidized bed. The weight of the product is usually approx. 710 g.

Application of lag time controlling layer (semipermeable membrane).

A coating suspension is made according to the following formula;

Ethylcellulose, 10 cps	10 g
Talc	23 g
EtOH (99.5%)	1000 g

The ethylcellulose is dissolved in the ethanol during stirring, then the talc is added. Spraying of the suspension onto 150 g of pellets from above (0.61-0.71 mm obtained by sieving) is done in a Wurster equipped fluidized bed. The weight of the obtained pellets is usually approx. 175 g.

Application of enteric coating layer.

Pellets from above are enteric coated in a fluidized bed with a coating dispersion according to below;

Eudragit L30 D-55 (30 % w/w dispersion)	73.3g
Triethyl citrate (TEC)	6.6 g
Glycerol monostearate (GMS)	0.3 g
Polysorbate 80	0.03 g
Purified water	40.4 g

A homogenous coating dispersion is prepared by dispersing polysorbate 80 and glycerol monostearate in water. Tritehylcitrate is dissolved in the Eudragit dispersion and thereafter the two dispersions are mixed to obtain the coating dispersion.

The coating dispersion is applied onto 120 g pellets, using a Wurster equipped fluidized bed. The weight of the enteric coated pellets is usually approx. 140 g.

Preparation of tablets

Tableting excipient for mixing with enteric coated pellets is prepared by mixing the following ingredients to homogeneity;

Tableting excipient;	
Microcrystalline cellulose special coarse grade PH 102	12.12 g
Microcrystalline cellulose PH 101	6.06 g

Polyvinyl pyrrolidone cross-linked	1.82 g
Sum:	20.00 g

Compression to tablets is done on a tablet machine equipped with 9x21 mm oval punches (giving elliptically shaped tablets). The tablets are prepared by first pre-compressing 404 mg of the misoprostol-containing granules and then filling a mixture consisting of approx. 270 mg S-Omeprazole magnesium salt comprising pellets (according to above) and 270 mg of the tableting excipient mix.

Example 7.

Enteric coated tablet comprising 45 mg omeprazole (magnesium salt) in a hydrophilic matrix, having an outer fast dissolving coat upon the enteric coat, the outer coat comprises approx. 220 µg of misoprostol.

Extended release tablets comprising omeprazole Mg-salt (approx. 45 mg).

Granules for tablet cores are made according to the following composition (parts by weight);

Omeprazole Mg-salt	80
Hydroxypropyl methylcellulose 50 cps	300
Polyvinyl pyrrolidone (PVP) K-90	40
Ethanol 99.5% (w/v)	400

The PVP is dissolved in the alcohol. The other two ingredients are mixed and then moistened with the PVP-solution in a mixer. Thereafter the obtained mass is dried in a drying oven at 50°C. After milling in an oscillating mill through a 1.0 mm screen the obtained granules are mixed with tablet lubricant, according to the following composition (parts by weight);

Granules for tablet core	412
Sodium stearyl fumarate (Pruv®)	4

The ingredients are mixed whereafter the mixture is compressed to tablets (9 mm in diameter) having an average weight of 265 mg, on a tableting machine.

Separating layer coated tablets

Obtained tablets are coated first with a separating layer in e.g. a rotating drum coating apparatus, with a coating suspension of the following composition;

EtOH 99.5% (w/v)	85	parts by weight
Water purified	85	parts by weight
Hydroxypropyl methylcellulose 6 cps	10	parts by weight
Talc, micronized	2	parts by weight
Sum:	182	parts.

The coating of the tablets is continued until average tablet weight is approx 274 mg.

Enteric coated tablets

The tablets coated with a separating layer are coated with an enteric coating layer in the same equipment as for the preceeding coating step. The coating solution to be used has the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55®)	19	parts by weight
Cetanol	1	parts by weight
Acetone	182	parts by weight
Ethanol (95% w/v)	78	parts by weight
Sum:	280	parts

Separating layer coated tablets are processed and the coating is continued until average tablet weight is 293 mg.

Enteric coated tablets coated with misoprostol layer

The enteric coated omeprazole Mg-salt tablets are coated with a solution of HPMC and misoprostol in e.g. a rotating drum coating apparatus, using the following composition;

Dispersion	
EtOH 95% (w/v)	125 parts by weight
Misoprostol	0.46 parts by weight
Water, purified	125 parts by weight
Hydroxypropyl methyl cellulose (HPMC) 6 cps	5.34 parts by weight
Colloidal silica (Aerosil RTM)	0.50 parts by weight

First the misoprostol is dissolved in the ethanol and then the water is added. The HPMC is admixed and dissolved. Finally the Aerosil™ is dispersed in the solution.

The coating is continued, until the average tablet weight is 296 mg.

Example 8.

Enteric coated tablet comprising 20 mg omeprazole (magnesium salt) in a hydrophilic matrix, having an outer hydrophilic matrix layer upon the enteric coat, the outer layer comprises 200 µg misoprostol.

Granules comprising omeprazole Mg-salt are prepared according to this recipe;

	mg/tablet
Omeprazole Mg-salt	22.5
Ethanol 95% (w/v)	90
Hydroxypropyl methyl cellulose (HPMC) 50 cps	50

Hydroxypropyl methyl cellulose (HPMC) 10000 cps	40
Polyvinyl pyrrolidone (PVP) K-90	6.5

The PVP is dissolved in the ethanol. This solution is poured on the mixed powders of the HPMC's and Omeprazole Mg-salt powder during continued mixing. The mass is dried on a tray at 50°C in a drying oven. After milling through a 0.8 mm screen the obtained granules are mixed with tablet lubricant according the following composition;

Granules	119 g
Sodium stearyl fumarate (Pruv®)	1 g

The mixing is performed in to homogeneity in a mixer, e.g. Kenwood. Then it is compressed to 6 mm in diameter tablets having an average weight of 120 mg on a tableting machine. The tablets are coated with a separating layer by using a solution of HPMC and coating, e.g. in a fluid bed coating apparatus or rotating drum coater, using the following composition;

EtOH 95% (w/v)	125	parts by weight
Water, purified	125	parts by weight
Hydroxypropyl methyl cellulose (HPMC) 6 cps	5.3	parts by weight

The HPMC is dissolved in the ethanol/water mixture. The coating is continued until average tablet weight has increased with 4 mg (i.e. if starting average weight is 120 mg, to 124 mg).

The obtained separating layer coated tablets are coated with an enteric coating layer in the same equipment as for the preceeding coating step. The coating solution has the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55)	16 parts by weight

Cetanol		1 parts by weight
Acetyl tributyl citrate		1 part by weight
Acetone		153 parts by weight
Ethanol (95% w/v)		65 parts by weight
	Sum:	236 parts by weight

The tablets are coated until average tablet weight is 133 mg. The obtained enteric coated extended release omeprazole Mg salt tablets are dry coated in a suitable tableting machine with a granulate comprising HPMC and misoprostol prepared using the following composition;

Misoprostol	0.2 parts by weight
Ethanol 95% (w/v)	200 parts by weight
Hydroxypropyl methyl cellulose (HPMC) 50 cps	200 parts by weight

First the misoprostol is dissolved in the ethanol. Then the solution is poured on the HPMC powder during mixing. The mass is dried using mild conditions. Obtained dried granules are milled in an oscillating granulator equipped with a 1.0 mm screen.

For the manufacturing of each dry coated extended release tablet, one enteric coated omeprazole Mg-salt tablet and 200 mg of misoprostol comprising extended release granulate is used, and compressed with 10 mm diameter punches.

Example 9.

Capsule formulation comprising 20 mg pantoprazole and 400 μg of misoprostol, the latter comprised in a hydrophilic matrix plug.

Pantoprazole pellets are prepared as described in Example 5, with lansoprazole replacing pantoprazole.

Extended release plug comprising misoprostol is prepared by first making a granulation according to this recipe;

Misoprostol	0.4 parts by weight
Ethanol 95% (w/v)	110 parts by weight
Hydroxypropyl methyl cellulose 50 cps	118 parts by weight

The misoprostol is dissolved in 110 parts of ethanol. This solution is poured on the HPMC powder during mixing. The mass is dried under mild conditions. The particle size of the dried granules is reduced until all granules pass a 0.8 mm sieve. Thereafter the lubricant sodium stearyl fumarate is admixed, according to following recipe;

Granules according to above	118.4 parts by weight
Sodium stearyl fumarate	1.6 parts by weight
sum	120.0 parts by weight

The mixing is performed to homogeneity in a mixer. Then it is compressed to 6 mm in diameter plugs (tablets) having an average weight of 120 mg on a tableting machine.

Capsule filling;

One plug according to above and 95 mg pantoprazole comprising pellets are filled into a hard gelatine capsule of size no 1.

Example 10.

Enteric coated, layered tablet with dual pulsed release of S-omeprazole magnesium salt (2 x approx.15 mg), having an outer fast dissolving coat upon the enteric coat, the outer layer comprises 220 µg of misoprostol.

Granules

Granules for tablet cores are made according to the following composition;

	parts by weight
S-omeprazole Mg-salt	229
Microcrystalline cellulose, Avicel PH 101	151
Microcrystalline cellulose, Avicel PH 102 sp. Coarse grade	400
L-HPC	256
PVP-XL	302
Sodium laurylsulphate (SLS)	30
Water purified	1060

A granulating solution is prepared by dissolving the SLS in 460 parts of purified water. The powders above are mixed in a mixer after which the solution is added in an even stream. Thereafter approx. 600 parts of water is added during continued mixing, to give satisfactory consistence to the mass. The mass is dried in a drying oven at 50°C over night.

Preparation of tablet cores

After milling through a 1.0 mm screen the obtained granules are mixed with tablet lubricant, sodium chloride, and an additional amount of swellable substance, according the following composition;

	parts by weight
Granules for homogenous tablet core	400
Sodium chloride (passing 0.3 mm)	80
Sodium stearyl fumarate (Pruv®)	8
Polyvinyl pyrrolidone cross-linked (PVP-XL)	20

The mixing is performed in to homogeneity in a mixer, e.g. Kenwood. Then it is compressed to 6 mm in diameter tablets having an average weight of 126 mg on a tableting machine.

Application of lag time controlling layer (semipermeable membrane).

The tablets are coated in a Wurster equipped fluidized bed coating apparatus with a coating suspensio following composition;

EtOH 99.5% (w/v)		291 parts by weight
Ethyl cellulose N-10		11 parts by weight
Talc, micronized		7 parts by weight
	Sum:	309 parts

The tablets are coated and the coating is continued until average tablet weight is 134 mg.

Application of drug containing layer

The obtained tablets are coated in the same equipment as above with a coating suspension of the following composition;

S-omeprazole Mg-salt		20 parts by weight
Hydroxypropyl methylcellulose 6 cps		13 parts by weight
Ethanol 99%		128 parts by weight
Water purified		128 parts by weight
	Sum:	289 parts.

The tablets are coated and the coating is continued until the average tablet weight is 162 mg.

Separating layer coated tablets

Obtained tablets are coated first with a separating layer, in e.g. a rotating drum coating apparatus, with a coating suspension of the following composition;

EtOH 99.5% (w/v)		85 parts by weight
Water purified		85 parts by weight
Hydroxypropyl methylcellulose 6 cps		10 parts by weight
Talc, micronized		2 parts by weight
	Sum:	182 parts.

The coating of the tablets is continued until average tablet weight is approx 166 mg.

Application of enteric coating layer

The obtained tablets are coated with an enteric coating layer in the same equipment as for the preceeding coating step. The coating solution has the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55)		16 parts by weight
Cetanol		1 parts by weight
Acetone		153 parts by weight
Ethanol (95% w/v)		65 parts by weight
	Sum:	235 parts by weight

The tablets are coated and the coating is continued until average tablet weight is 177 mg.

The enteric coated dual pulsed release S-omeprazole Mg salt tablets are coated with a solution of HPMC and misoprostol e.g. in a fluid bed coating apparatus or rotating drum coater, using the following composition;

Tablets (according to above)	100	parts by weight

Solution;		
EtOH 95% (w/v)	125	parts by weight
Misoprostol	0.46	parts by weight
Water, purified	125	parts by weight
Hydroxypropyl methyl cellulose (HPMC) 6 cps	5.34	parts by weight
Colloidal silica (Aerosil™)	0.50	parts by weight

First the misoprostol is dissolved in the ethanol and then the water is added. The HPMC is admixed and dissolved. Finally the Aerosil™ is dispersed in the solution.

The coating is continued until average tablet weight has increased with 3 mg (i.e. if starting average weight is 177 mg, to 180 mg).

Example 11.

Two-layer tablet with pellets comprising 200 µg misoprostol and pellets comprising 20 mg omeprazole (magnesium salt) mixed with tableting excipients in one layer, and the other layer comprises 30 mg nifedipine in a hydrophilic matrix.

Extended release granules comprising nifedipine was prepared according to this recipe;

Nifedipine	30	g
Polyoxyl 40 hydrogenated castor oil	30	g
Ethanol 99.5% (w/v)	300	g
Ethyl cellulose N-10	20	g
Propyl gallate	0.06	g
Hydroxypropyl methyl cellulose 50 cps	175	g
Sodium aluminium silicate	75	g
Sodium stearyl fumarate	6	g

Nifedipine, polyoxyl 40 hydrogenated castor oil and propyl gallate are charged into the ethanol. This mixture is heated and stirred until a solution is formed, keeping the temperature of the mixture/solution at maximum 70°C. Then the ethyl cellulose is added and dissolved. The obtained solution is poored on a mixture of the HPMC and the sodium aluminium silicate powders during mixing. The mass is dried in an explosion safe drying cabinet, whereafter it is milled in an oscillating granulator having a screen with 1 mm openings. The obtained granules are mixed with the lubricant sodium stearyl fumarate for 2 minutes.

Enteric coated pellets comprising omeprazole magnesium salt were prepared as described in Example 1.

Misoprostol pellets are prepared by dissolving misprostol in ethanol and then mixing porous silica particles with this solution, according to the following recipe;

Misoprostol	0.16 parts by weight
Silica particles, porous, appr diameter 150 μm	53.14 parts by weight
Ethanol 95% (w/v)	42.5 parts by weight

The mass is dried under mild conditions. Obtained misoprostol pellets contain approx. 3.75 mg misprostol per gram.

Tableting excipients for mixing with omeprazole and misoprostol pellets are prepared by mixing the following ingredients to homogeneity;

Tableting excipient;

Microcrystalline cellulose special coarse grade PH 102	12.12 parts by weight
Microcrystalline cellulose PH 101	6.06 parts by weight
Polyvinyl pyrrolidone cross-linked	1.82 parts by weight

Sum:	20.00 parts by weight

Compression to tablets is done on a tablet machine equipped with 9x17 mm oval punches (giving elliptically shaped tablets). The tablets are prepared by first pre-compressing 336 mg of the nifedipine containing granules and then filling a mixture consisting of 100 mg omeprazol magnesium salt comprising pellets (according to above), 53 mg misoprostol containing pellets and 200 mg of the tableting excipient mix, giving a total tablet weight of 689 mg.

To protect the nifedipine in the tablets against photolytic degradation, the tablets are coated with a solution of HPMC and PEG having pigments dispersed therein, in a fluid bed coating apparatus or rotating drum coater, using the following composition;

Tablets (according to above)	336	parts by weight
Solution;		
Water purified	122	parts by weight
Hydroxypropyl methyl cellulose (HPMC) 6 cps	14	parts by weight
Polyethylene glycol (PEG) 6000	4	parts by weight
Titanium dioxide	2	parts by weight
Iron oxide yellow	2	parts by weight

The coating is continued until average tablet weight has increased with 15 - 20 mg.

Example 12.

Enteric coated pellets comprising approx. 225 mg/g S-omeprazole magnesium salt and misoprostol, approx. 3.5 mg/g pellet wherein the latter is positioned in an outer extended release layer.

Enteric coated pellets comprising S-omeprazole magnesium salt were prepared as described in Example 2.

The enteric coated pellets are coated with a solution of HPMC and misoprostol in a fluid bed apparatus, using the following composition;

Enteric coated pellets (according to above)	100	parts by weight
Solution;		
EtOH 95% (w/v)	300	parts by weight
Water, purified	50	parts by weight
Misoprostol	0.46	parts by weight
Hydroxypropyl methyl cellulose (HPMC) 50 cps	5.34	parts by weight
Colloidal silica (Aerosil™)	0.50	parts by weight

First the misoprostol is dissolved in the ethanol and then the water is added. Thereafter the HPMC is admixed and dissolved. Finally the Aerosil™ is dispersed in the solution. The obtained pellets are classified by sieving. The prepared pellets may be compressed into a multiple unit tablet as described in Example 5, or filled into a capsule suitable for the desired dose.

Claims

1. An oral pharmaceutical dosage form comprising a H^+, K^+-ATPase inhibitor and a gastric antisecretory prostaglandin analogue compound and optionally pharmaceutically acceptable excipients, wherein the dosage form is in the form of a fixed unit dosage form comprising at least these two pharmaceutically active components.

2. A dosage form according to claim 1, wherein the dosage form is a tablet formulation.

3. A dosage form according to claim 1, wherein the dosage form is a capsule formulation.

4. A dosage form according to any of claims 1-3, wherein the H^+, K^+-ATPase inhibitor compound is protected by an enteric coating layer, and optionally a separating layer is applied under the enteric coating separating the H^+, K^+-ATPase inhibitor from the enteric coating layer.

5. A dosage form according to claim 1, wherein the fixed dosage form in addition to the H^+, K^+-ATPase inhibitor and the gastric antisecretory prostaglandin analogue comprises a calcium channel blocking agent.

6. A dosage form according to any of claims 1-5, wherein the H^+, K^+-ATPase inhibitor is omeprazole, an alkaline salt thereof, one of its single enantiomer or an alkaline salt thereof.

7. A dosage form according to claim 6, wherein the H^+, K^+-ATPase inhibitor is omeprazole magnesium salt.

8. A dosage form according to claim 6, wherein the H^+, K^+-ATPase inhibitor is S-omeprazole magnesium salt.

9. A dosage form according to any of claims 1-5, wherein the H^+, K^+-ATPase inhibitor is lansoprazole, or one of its single enantiomers or a pharmaceutically acceptable salt thereof.

10. A dosage form according to any of claims 1-5, wherein the H^+, K^+-ATPase inhibitor is pantoprazole, or one of its single enantiomers or a pharmaceutically acceptable salt thereof.

11. A dosage form according to one of claims 1-10, wherein the gastric antisecretory prostaglandin analogue compound is misoprostol, enisoprost, enprostil or one of the single enantiomers thereof or a pharmaceutical acceptable salt thereof.

12. A dosage form according to any of claims 1-11, wherein the amount of the H^+, K^+-ATPase inhibitor is in the range of 1-200 mg and the amount of the gastric antisecretory prostaglandin analogue is in the range of 80 - 1 000 μg.

13. A dosage form according to any of claims 1-12, wherein the amount of the H^+, K^+-ATPase inhibitor is in the range of 5-80 mg and the amount of the gastric antisecretory prostaglandin analogue is in the range of 100-800 μg.

14. A tableted dosage form according to claim 2, wherein the tablet consists of two different layers, a first layer comprising the H^+, K^+-ATPase inhibitor and a second layer comprising the gastric antisecretory prostaglandin analogue.

15. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising

a) the H^+, K^+-ATPase inhibitor in the form of enteric coating layered pellets,

b) the gastric antisecretory prostaglandin analogue compound and optionally

c) pharmaceutically acceptable excipients

compressed together into a tablet, whereby the enteric coating layer covering the individual pellets has mechanical properties such that the tableting of the pellets together with the gastric antisecretory prostaglandin analogue and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the enteric coating layered pellets.

16. A tableted dosage form according to claim 15, wherein the enteric coating of the individual pellets comprises a plasticized enteric coating layer material.

17. A tableted dosage form according to claim 15, wherein the enteric coating layered pellets are further covered with an over-coating layer comprising a film forming polymer and pharmaceutically acceptable excipients.

18. A tableted dosage form according to any of claims 15-17, wherein the tablet is divisible.

19. A tableted dosage form according to claim 2, wherein at least one part of the tablet is in the form of an extended release formulation.

20. A tablet dosage form according to claim 19, wherein the part of the tablet giving extended release is a hydrophilic matrix.

21. A tablet dosage form according to claim 19, wherein the part of the tablet giving extended release is a hydrophobic matrix.

22. A tablet dosage form according to claim 2, wherein the tablet consists of two different layers, a first layer comprising the H^+, K^+-ATPase inhibitor in the form of enteric

coating layered pellets compressed with tablet excipients into a layer, and a second layer giving an extended release of the incorporated gastric antisecretory prostaglandin analogue.

23. A tableted dosage form according to claim 2, wherein the tablet comprises enteric coating layered pellets of the H^+, K^+-ATPase inhibitor layered with a further layer comprising the gastric antisecretory prostaglandin analogue, and the layered pellets are compressed with tablet excipients to a tablet.

24. A tableted dosage form according to claim 23, wherein the pellets before compression to a tablet is covered by a pigmented film coating layer, or the compressed tablet is covered by a pigmented tablet coat.

25. A tablet dosage form according to claim 2, wherein the tablet consists of two types of layered pellets, the first type consists of enteric coating layered pellets comprising the H^+, K^+-ATPase inhibitor and the second type consists of pellets comprising the gastric antisecretory prostaglandin analogue, all pellets are compressed together with tablet excipients to a tablet.

26. A tablet dosage form according to claim 22, wherein the tablet consists of enteric coating layered pellets comprising the H^+, K^+-ATPase inhibitor, and pellets comprising the gastric antisecretory prostaglandin analogue incorporated in a matrix giving an extended release of the prostaglandin analogue.

27. A dosage form according to claim 3, wherein the capsule comprises two types of layered pellets, the first type consists of enteric coating layered pellets comprising the H^+, K^+-ATPase inhibitor and the second type consists of pellets comprising the gastric antisecretory prostaglandin analogue, all pellets and optionally pharmaceutically acceptable excipients are filled in the capsule.

28. A process for the manufacture of a fixed dosage form comprising a H^+, K^+-ATPase inhibitor and one or more gastric antisecretory prostaglandin analogue(s) in a capsule, characterized in that the H^+, K^+-ATPase inhibitor is prepared in the form of enteric coating layered pellets, and the gastric antisecretory prostaglandin analogue is prepared in the form of pellets coating layered with an extended release film, the pellets are mixed, optionally with pharmaceutically acceptable excipients, and the mixture is filled in to capsules.

29. A process for the manufacture of a fixed dosage form comprising a H^+, K^+-ATPase inhibitor and one or more gastric antisecretory prostaglandin analogues in a multiple unit tableted dosage form, characterized in that the H^+, K^+-ATPase inhibitor is prepared in the form of enteric coating layered pellets and these pellets are mixed with pellets comprising the gastric antisecretory prostaglandin analogue, and optionally pharmaceutically acceptable tablets excipients, whereafter the mixture is compressed into multiple unit tablets without causing any significant change of the acid resistance of the enteric coating layered pellets.

30. A process for the manufacture of a fixed dosage form comprising a H^+, K^+-ATPase inhibitor and one or more gastric antisecretory prostaglandin analogues in a multiple unit tableted dosage form, characterized in that the H^+, K^+-ATPase inhibitor is prepared in the form of enteric coating layered pellets and the gastric antisecretory prostaglandin analogue is prepared in the form of coating layered pellets wherein the coating layer is an extended release layer, the pellets are mixed, optionally with pharmaceutically acceptable tablet excipients, and compressed into tablets without causing any significant change of the acid resistance of the enteric coating layered pellets.

31. A method for the treatment and profylaxis of gastrointestinal disorders by administering to a host in need thereof a therapeutic effective dosage form according to any of claims 1-27.

32. A method for avoiding gastrointestinal side-effects normally associated with gastric antisecretory prostaglandin analogue medicament treatment in mammals and man by administering to a host in need thereof a therapeutically effective dosage form according to any of claims 1-27.

33. Use of a dosage form according to any of claims 1-27 in the manufacture of a medicament for treatment or profylaxis of gastrointestinal diseases.

34. Use of a dosage form according to any of claims 1-27 in the manufacture of a medicament for avoiding gastrointestinal side-effects normally associated with gastric antisecretory prostaglandin analogue treatment.

35. A combination of a H^+, K^+-ATPase inhibitor, a gastric antisecretory prostaglandin analogue and a calcium channel blocking agent in the treatment of gastrointestinal diseases.

36. A blister pack comprising a H^+,K^+-ATPase inhibitor medicament and a gastric antisecretory prostaglandin analogue medicament.

37. A blister pack according to claim 36 comprising an additional medicament which is a calcium channel blocking agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02315

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/44, A61K 31 /557
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Digestive Diseases and Sciences, Volume 42, No. 8, August 1997, Akira Tari et al, "Effect of Enprostil on Omeprazole-Induced Hypergastrinemia and Inhibition of Gastric Acid Secretion in Peptic Ulcer Patients" pages 1741 - 1746 --	1-30,33-37
X	Digestive Diseases and Sciences, Volume 39, No. 3, March 1994, J.L. Meijer et al, "Effect of Synthetic Prostaglandin E2 Analog Enprostil on Omeprazole-Induces Hypergastrinemia and Hyperpepsinogenemia" pages 609 - 616 --	1-30,33-37

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2000	16 -05- 2000
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/LR Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02315

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Italian Journal of Gastroenterology and Hepatology Volume 30, No. 4, August 1998, Cheli R. et al, "Pre-treatment with misoprostol increases the efficacy of omeoprazole plus amoxycillin to cure Helicobacter pylori infection. A pilot study" pages 558 - 563 --	1-30,33-37
A	Gastroenterology, Volume 102,1992 Richard N. Fedorak et al, "Verapamil Alters Eicosanoid Synthesis and Accelerates Healing During Experimental Colitis in Rats" pages 1229 - 1235 -- --------	5,35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/02315

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 31-32
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 401/12, A61K 31/44 — A1

(11) International Publication Number: **WO 00/44744**

(43) International Publication Date: 3 August 2000 (03.08.00)

(21) International Application Number: PCT/SE00/00087

(22) International Filing Date: 18 January 2000 (18.01.00)

(30) Priority Data:
9900274-3 28 January 1999 (28.01.99) SE

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: POTASSIUM SALT OF (*S*)-OMEPRAZOLE

(57) Abstract

The present invention relates to a novel form of 5- methoxy- 2- [[(4- methoxy- 3,5- dimethyl- 2- pyridinyl) methyl] sulfinyl] -1H- benzimidazole, known under the generic name omeprazole. More specifically, it relates to a novel crystalline form of the potassium salt of the (*S*)- enantiomer of 5- methoxy- 2- [[(4- methoxy- 3,5- dimethyl- 2- pyridinyl) methyl] sulfinyl] -1H- benzimidazole. The present invention also relates to processes for preparing such a form of the potassium salt of (*S*)- omeprazole and pharmaceutical compositions containing it.

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POTASSIUM SALT OF (*S*)-OMEPRAZOLE

Field of the invention

The present invention relates to a novel form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, known under the generic name omeprazole. More specifically, it relates to a novel crystalline form of the potassium salt of the (*S*)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.The present invention also relates to a process for preparing such a form of potassium salt of (*S*)-omeprazole and pharmaceutical compositions containing it.

Background of the invention and prior art

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts thereof, are described in EP 5129. The specific alkaline salts of omeprazole are disclosed in EP 124 495. Omeprazole is a proton pump inhibitor, *i.e.* effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for prevention and treatment of gastric-acid related diseases in mammals and especially in man.

Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom is the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the (*R*)- and (*S*)-enantiomer of omeprazole, herein referred to as (*R*)-omeprazole and (*S*)-omeprazole. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (-)-enantiomer of the non-salt

form were found to have *R* and *S* configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

Certain salts of the single enantiomers of omeprazole and their preparation are disclosed in WO 94/27988. These compounds have improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation.

WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and structually related compounds as well as salts thereof. WO 96/01623 discloses pharmaceutical dosage forms comprising for instance magnesium salts of (*R*)- and (*S*)-omeprazole.

WO 98/54171 discloses a process for the preparation of the trihydrate of magnesium salt of (*S*)-omeprazole, wherein the potassium salt of (*S*)-omeprazole is used as an intermediate. The potassium salt of (*S*)-omeprazole, according to the prior art, crystallizes as a methanol solvate.

Certain salts of of (*S*)-omeprazole, such as the potassium salt, are in general suitable compounds for i.v.-administration due to their intrinsic properties, such as high stability and high solubility in water. Methanol solvates are however not suitable for i.v.-administration, since the concomitant administration of methanol could be fatal for the receiver. Therefore there exists a need for a potassium salt of (*S*)-omeprazol that is free from methanol.

The novel form of the potassium salt of (*S*)-omeprazole according to the present invention is hereinafter referred to as the potassium salt of (*S*)-omeprazole form B. The prior art form of the potassium salt of (*S*)-omeprazole disclosed in WO 98/54171 is hereinafter referred to as the potassium salt of (*S*)-omeprazole form A.

Brief description of the drawings

Figure 1 is an X-ray powder diffractogram of the potassium salt of (*S*)-omeprazole prepared according to the present invention, i.e. form B.

Figure 2 is an X-ray powder diffractogram of the potassium salt of (*S*)-omeprazole prepared according to example 2 in WO 98/54171, i.e. form A.

Description of the invention

It has surprisingly been found that the potassium salt of (*S*)-omeprazole occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure potassium salt of (*S*)-omeprazole form B.

The potassium salt of (*S*)-omeprazole form B is advantageous because it is hydrate form, while the previous known form A is methanol solvate. The potassium salt of (*S*)-omeprazole form B is especially suitable for intravenous administration. The potassium salt of (*S*)-omeprazole form B is further characterized by being crystalline, and preferably being highly crystalline.

The potassium salt of (*S*)-omeprazole form B, obtained according to the present invention, is substantially free from other forms of potassium salts of (*S*)-omeprazole, such as the corresponding form A described in the prior art .The potassium salt of (*S*)-omeprazole form B obtained according to the present invention is also substantially free from potassium salts of (*R*)-omeprazole.

The potassium salt of (*S*)-omeprazole form B is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram , but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other forms of potassium salt of (*S*)-omeprazole and accordingly, the potassium salt

of (*S*)-omeprazole form B is easily distinguishable from any other crystal forms of potassium salts of (*S*)-omeprazole disclosed in prior art. With the expression "any form" is meant anhydrates, hydrates, solvates, amorphous forms, and polymorphs. Such examples of any forms of potassium salt of (*S*)-omeprazole includes, but are not limited to, anhydrates, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates, such as methanolates and ethanolates, amorphous forms and polymorphs.

The potassium salt of (*S*)-omeprazole form B may also be characterized by its unit cell.

In a further aspect, the present invention provides a process for the preparation of the potassium salt of (*S*)-omeprazole form B which comprises the step of converting (*S*)-omeprazole into the corresponding potassium salt in toluene or dichloromethane by treatment with a potassium source, such as potassium hydroxide or potassium methylate, followed by isolation of the formed salt.

The crude (*S*)-omeprazole used in the process can for example be prepared by oxidizing 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole into (*S*)-omeprazole, with an oxidizing agent and a chiral titanium complex, optionally in the presence of a base in an organic solvent, such as toluene or dichloromethane, as is described in the prior art, see WO 98/54171.

The potassium salt of (*S*)-omeprazole form B, prepared according to the present invention is analyzed, characterized and differentiated from the previous known form A by X-ray powder diffraction, a technique which is known per se. Another suitable technique to analyze, characterize and differentiate the potassium salt of (*S*)-omeprazole form B from the corresponding form A is by conventional FT-IR.

The amount of water in the potassium salt of (*S*)-omeprazole form B is determined by thermogravimetric analysis (TGA), a technique which is known per se.

The potassium salt of (*S*)-omeprazole form B is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for treatment of gastric-acid related conditions in mammals and especially in man, including *e.g.* reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable *e.g.* in patients on non-steroidal anti-inflammatory drug (NSAID) therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The potassium salt of (*S*)-omeprazole form B may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to treat stress ulceration. Further, the potassium salt of (*S*)-omeprazole form B may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these. The potassium salt of (*S*)-omeprazole form B may also be used for treatment of inflammatory conditions in mammals, including man.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the potassium salt of (*S*)-omeprazole form B, according to the present invention. For example, peroral or parenteral formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like. The potassium salt of (*S*)-omeprazole form B is, because of being highly soluble in water, especially suitable for parenteral formulations, such as i.v.

According to the invention there is further provided a pharmaceutical composition comprising the potassium salt of (*S*)-omeprazole form B, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of *Helicobacter* infections. The invention also provides the use of the potassium salt of (*S*)-omeprazole form B in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of

treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the potassium salt of (*S*)-omeprazole form B.

The compositions of the invention include compositions suitable for peroral or parenteral administration. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods known in the art of pharmacy.

In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of the potassium salt of (*S*)-omeprazole form B in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below. Such higher and lower doses are within the scope of the present invention.

In general, a suitable dosage form may cover a dose range from 5 mg to 120 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage range is from 5 mg to 100 mg, and more preferred 10 mg to 80 mg. A suitable administration dose is 20 mg to 40 mg for intravenous administration as well as oral administration

The compound of the invention may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques. Especially suitable oral formulations are described in WO 96/01623 and EP 247 983, the disclosures of which are hereby incorporated as a whole by reference.

Combination therapies comprising the potassium salt of (*S*)-omeprazole form B and other active ingredients in separate dosage forms may also be used. Examples of such active ingredients include anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

The examples which follow will further illustrate the preparation of the compound of the invention, *i.e.* the potassium salt of (*S*)-omeprazole form B, but are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

Examples

Potassium salt of (S)-omeprazole form B

A solution of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (67 mmol) in toluene (4 mL/g 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole) was charged with water (0,9 mmol) and D-(-)-diethyl tartrate (14 mmol) at 50°C. After stirring for 20 minutes, titanium(IV) isopropoxide (6,5 mmol) was added and the solution was stirred for approximately 50 minutes. The reaction mixture was temperated to 35°C and N,N-diisopropylethylamine (10 mmol) was added. Cumene hydroperoxide (74 mmol) was then charged to the solution while keeping the temperature at approximately 35°C.

After 3 hours, the reaction mixture was diluted with toluene (2 mL/g 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole) and potassium methoxide (26 mmol) was added as a slurry in toluene (8 mL/g KOMe).
The obtained crystals were filtered off and dried (36°C, vacuum) over night.
Yield 0,72 g (1,9 mmol; 7 % in respect of KOMe).

Content of solvents as obtained with Karl-Fischer titration and GC respectively (% w/w)

Water 3,4

Methanol 0,01

TGA

Approximately 2 % (w/w) of the water content is incorporated in the crystal lattice (*i.e.* ~0,5 H_2O / molecule of potassium salt of (*S*)-omeprazole form B)

XRD

The X-ray powder diffractogram of the product measured from 1-40° in 2θ with $CuK\alpha_1$ radiation shows the following characteristic list of peaks:

d-value [Å]	*Intensity*
9.6	very strong
8.0	strong
7.9	strong
7.5	weak
7.3	weak
7.2	very strong
5.9	strong
5.6	strong
5.2	strong
5.1	very strong
4.88	weak
4.83	weak
4.71	weak
4.67	weak
4.55	medium
4.49	strong
4.39	strong
4.15	weak

d-value [Å]	*Intensity*
4.10	weak
3.95	weak
3.74	very strong
3.67	medium
3.58	strong
3.55	medium
3.47	strong
3.40	weak
3.27	strong
3.20	medium
3.15	medium
3.10	weak
3.03	weak
2.98	medium
2.87	medium
2.85	medium
2.38	medium
2.30	weak

In addition the diffractogram contains several weak peaks that have been omitted for clarity.

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractogram of the potassium salt of (*S*)-omeprazole form B. The relative intensities are less reliable and instead of numerical values the following definitions are used;

% Relative Intensity	Definition
25-100	vs (very strong)
10-25	s (strong)
3-10	m (medium)
1-3	w (weak)

CLAIMS

1. The potassium salt of (*S*)-omeprazole form B, characterized in being a hydrate form.

2. The potassium salt of (*S*)-omeprazole form B according to claim 1, characterized in being crystalline.

3. The potassium salt of (*S*)-omeprazole form B, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values;

d-value [Å]	*Intensity*
9.6	very strong
8.0	strong
7.9	strong
7.5	weak
7.3	weak
7.2	very strong
5.9	strong
5.6	strong
5.2	strong
5.1	very strong
4.88	weak
4.83	weak
4.71	weak
4.67	weak
4.55	medium
4.49	strong
4.39	strong
4.15	weak

d-value [Å]	*Intensity*
4.10	weak
3.95	weak
3.74	very strong
3.67	medium
3.58	strong
3.55	medium
3.47	strong
3.40	weak
3.27	strong
3.20	medium
3.15	medium
3.10	weak
3.03	weak
2.98	medium
2.87	medium
2.85	medium
2.38	medium
2.30	weak

4. A process for the preparation of potassium salt of (*S*)-omeprazole form B as defined in any of claims 1-3, which comprises the step of converting (*S*)-omeprazole into the corresponding potassium salt in toluene or dichloromethane by treatment with a potassium source, such as potassium hydroxide or potassium methylate, followed by isolation of the formed salt.

5. A process according to claim 4, comprising the additional step of oxidizing 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole, with an oxidizing agent and a chiral titanium complex, optionally in the presence of a base in an organic solvent, such as toluene or dichloromethane, to obtain (*S*)-omeprazole

6. A pharmaceutical formulation comprising the potassium salt of (*S*)-omeprazole form B as defined in any of claims 1-3 in admixture with a pharmaceutically acceptable excipient.

7. A pharmaceutical formulation suitable for i.v. administration comprising the potassium salt of (*S*)-omeprazole form B as defined in any of claims 1-3 in admixture with a pharmaceutically acceptable excipient.

8. The use of potassium salt of (*S*)-omeprazole form B as defined in any of claims 1-3, as active ingredient in the manufacture of medicament for use in treatment of gastrointestinal disorders.

9. The use of the potassium salt of (*S*)-omeprazole form B as defined in any of claims 1-3 in the manufacture of a pharmaceutical formulation for i.v. administration.

10. A method of treatment of gastrointestinal disorders which comprises administration of a therapeutically effective amount of potassium salt of (*S*)-omeprazole form B as defined in any of claims 1-3, to a patient suffering from gastrointestinal disorders.

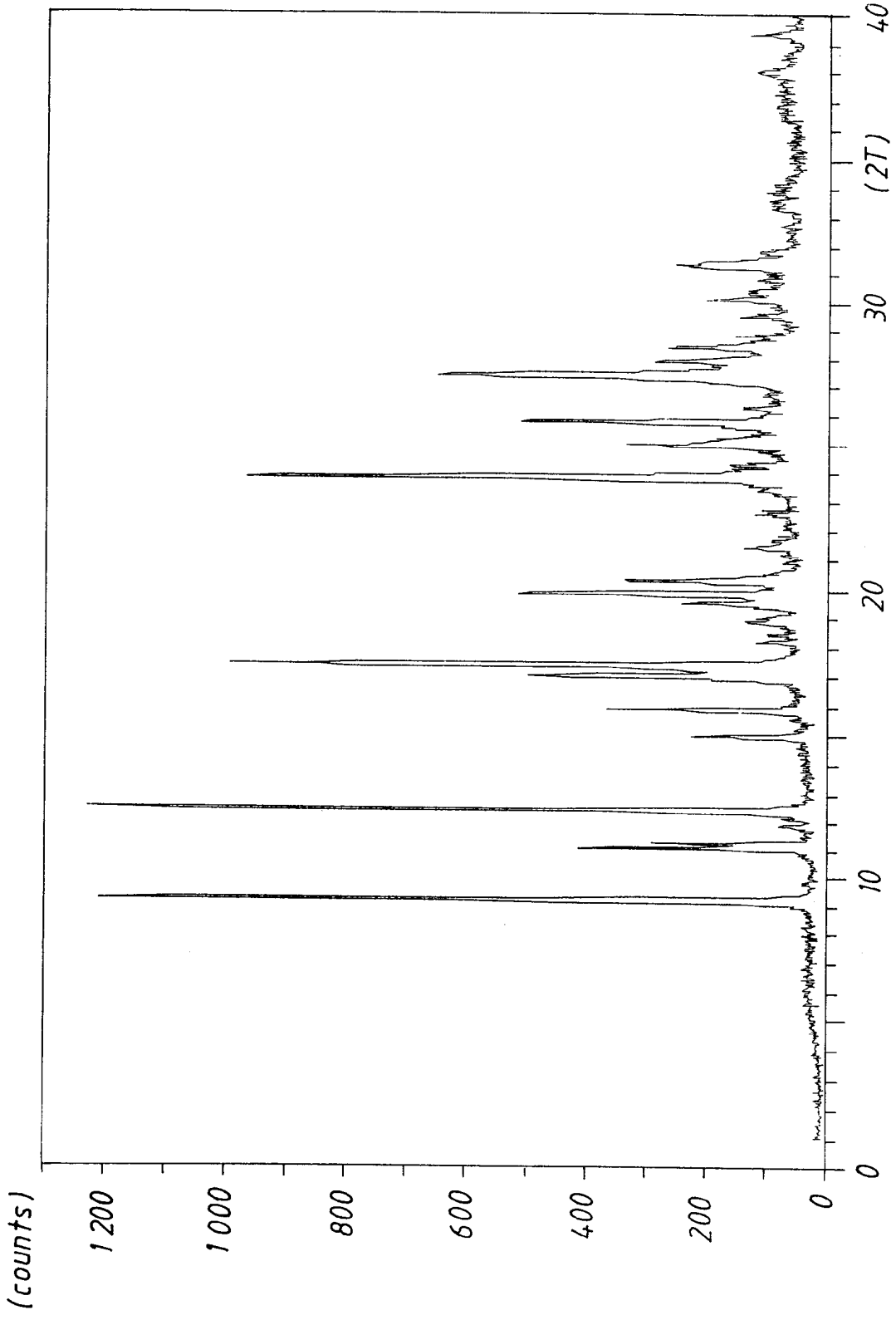
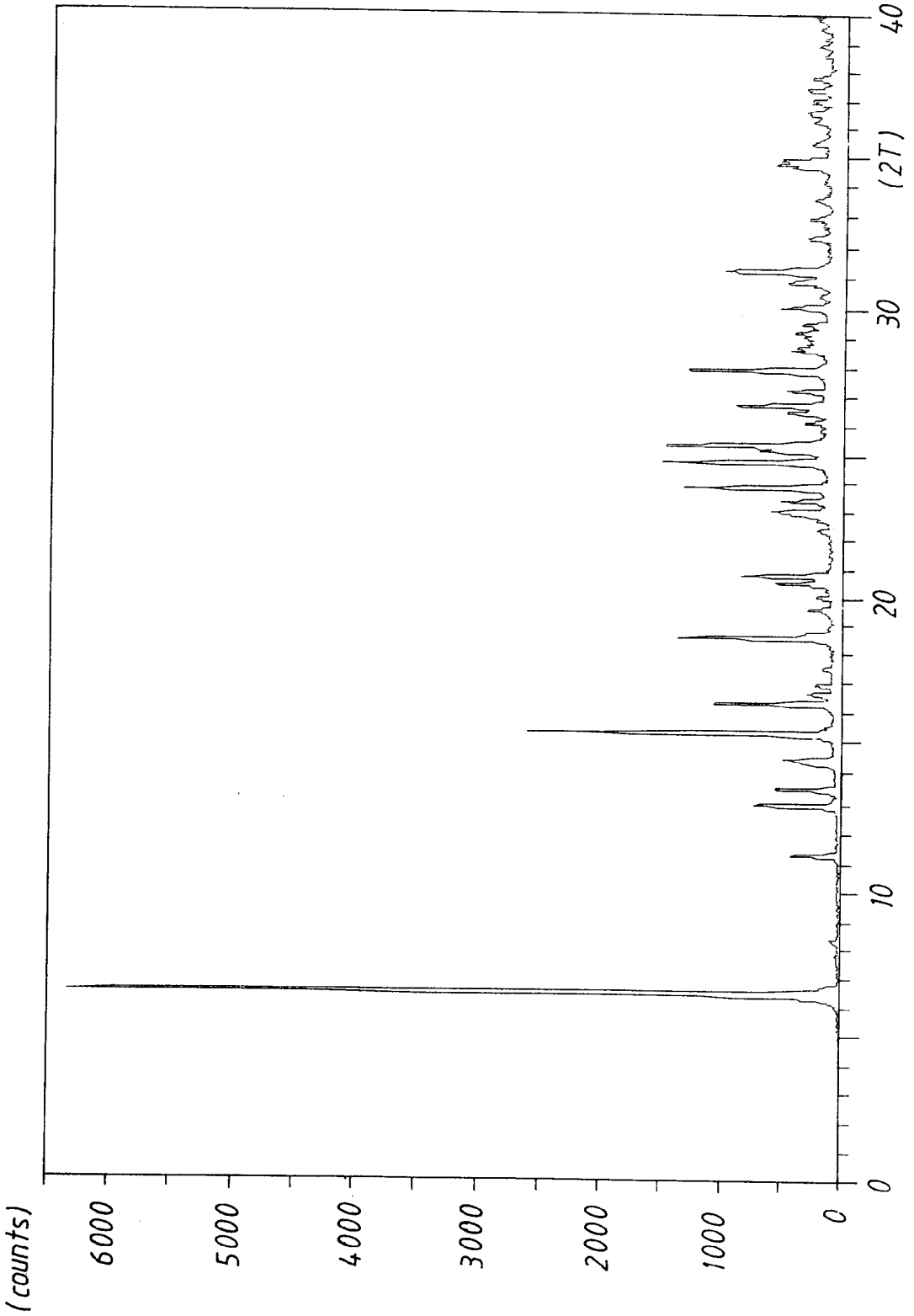


Fig. 1

Fig. 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00087

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/12, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9854171 A1 (ASTRA AKTIEBOLAG), 3 December 1998 (03.12.98) --	1-9
A	WO 9427988 A1 (ASTRA AKTIEBOLAG), 8 December 1994 (08.12.94) --	1-9

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"P" document published prior to the international filing date but later than the priority date claimed
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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 May 2000	19 -05- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/0087

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

02/12/99

International application No.
PCT/SE 00/00087

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9854171 A1	03/12/98	AU 7793598 A	30/12/98
		AU 7849898 A	03/07/98
		HR 980263 A	28/02/99
		SE 510650 C	14/06/99
		SE 9702065 A	01/12/98
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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/505, A61P 3/06 — A1

(11) International Publication Number: WO 00/45817

(43) International Publication Date: 10 August 2000 (10.08.00)

(21) International Application Number: PCT/GB00/00278

(22) International Filing Date: 1 February 2000 (01.02.00)

(30) Priority Data:

9902593.4	6 February 1999 (06.02.99)	GB
9921063.5	8 September 1999 (08.09.99)	GB
9921064.3	8 September 1999 (08.09.99)	GB

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: DRUG COMBINATIONS COMPRISING (E) –7 – [4 –(4 –FLUOROPHENYL) –6 – ISOPROPYL –2 – [METHYL (METHYLSULFONYL) AMINO] PYRIMIDIN –5 –YL] (3R,5S) –3,5 – DIHYDROXYHEPT –6 – ENOIC ACID AND AN INHIBITOR, INDUCER OR SUBSTRATE OF P450 ISOENZYME 3A4

(57) Abstract

The invention concerns safe non–interacting drug combinations of a 3–hydroxy –3– methylglutaryl coenzyme A (HMG–CoA) reductase inhibitor, which is (E)–7– [4–(4–fluorophenyl) –6– isopropyl –2– [methyl (methylsulfonyl) amino] pyrimidin–5–yl] (3R,5S)–3,5–dihydroxyhept –6–enoic acid or a pharmaceutically acceptable salt thereof (the Agent) and a drug which is either an inducer, inhibitor or a substrate of cytochrome P450, in particular cytochrome P450 isoenzyme 3A4. Particular combinations are useful in treating hyperlipidaemia in humans who are receiving immunosuppressive chemotherapy. A preferred combination is the Agent and a fibrate drug, the use of such a combination in treating hyperlipidaemia in mammals, and medicaments containing such a combination for use in such treatments.

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DRUG COMBINATIONS COMPRISING (E)-7-[4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-[METHYL(METHYLSULFONYL)AMINO]PYRIMIDIN-5-YL](3R,5S)-3,5-DIHYDROXYHEPT-6-ENOIC ACID AND AN INHIBITOR, INDUCER OR SUBSTRATE OF P450 ISOENZYME 3A4

The invention concerns safe non-interacting drug combinations of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, which is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof (the Agent) and a drug which is either an inducer, inhibitor or a substrate of cytochrome P450, in particular cytochrome P450 isoenzyme 3A4. Particular combinations are useful in treating hyperlipidaemia in humans who are receiving immunosuppressive chemotherapy. A preferred combination is the Agent and a fibrate drug, the use of such a combination in treating hyperlipidaemia in mammals, and medicaments containing such a combination for use in such treatments.

Hypercholesterolaemia is one of the strongest risk factors for atherosclerosis which is associated with coronary artery disease (including angina pectoris, myocardial infarction and mortality), stroke (including cerebro vascular accident and transient ischaemic attack) and peripheral arterial occlusive disease. Several types of hypercholesterolaemia exist. The magnitude of hypercholesterolaemia may have consequences for the therapy, but in general, any reduction of elevated plasma cholesterol levels is generally accepted to result in an improvement of the risk profile. Dietary improvement and increased exercise are essential first steps and should continue even if drug therapy is instituted, but the therapeutic potential of drug therapy is significantly larger. Several types of drug therapy for hypercholesterolaemia are currently available. Guidelines exist for the treatment of hypercholesterolaemia for example, American Heart Association (AHA) (Anon 1988), Updated Sheffield treatment tables (Heart (1998) 80 Supp.2 S1-S29) and Recommendations of the task force of the European Society of Cardiology Guidelines (Pyorala 1994).

HMG-CoA reductase inhibitors are the most widely used prescription medication for the treatment of hypercholesterolaemia. By inhibiting the rate-controlling step in cholesterol biosynthesis, these agents effectively lower the plasma concentrations of atherogenic particles containing cholesterol such as low-density lipoprotein (LDL-C) and very low-density

lipoprotein (VLDL-C). Partial inhibition of hepatic cholesterol synthesis causes up-regulation of hepatic membrane LDL-C receptors which are responsible for the clearance of LDL-C from the circulation. In addition, reduced hepatic synthesis of cholesterol is thought to result in a modest reduction in the secretion of VLDL-C particles by the liver. Clinical trials with certain HMG Co A-reductase inhibitors, such as in the Scandinavian Simvastatin Survival Study, confirm a reduction in cardiovascular morbidity and mortality with such agents, and may even promote regression of atherosclerotic vascular lesions. Various HMG Co A-reductase inhibitors are marketed, and are collectively referred to as 'statins'.

Despite the impressive benefits of statin therapy, less than optimal therapeutic results may be achieved in some subjects, particularly in the more severe classes of hypercholesterolaemia. This can be due to the occurrence of reversible increases in liver transaminase levels at higher dose levels of statins as well as differences in efficacy between different statins. Clinically important (>3 times upper limit of normal [ULN]) elevations in serum alanine aminotransferase [ALT]) have been reported for atorvastatin in 0.8 per cent of patients at low doses of atorvastatin and higher at raised doses (European Summary of Product Characteristics [SmPC] for atorvastatin [Lipitor™]). In all cases the effect is dose-related and reversible. In general it is the incidence of ALT increases which limits dose escalation of statins rather than a limit to further increases in efficacy.

The first generation statins (such as lovastatin, pravastatin and simvastatin - prodrug derivatives of fungal metabolites - and fluvastatin) are categorised in that they achieve only a limited cholesterol lowering affect before the dose administered is limited by elevations in serum ALT. Second generation "superstatins" (such as atorvastatin - synthetic compounds-structurally distinct from first generation compounds) inhibitors are categorised in that they lower cholesterol levels to a much higher degree than the earlier first generation of statins before their dose is limited by serum ALT levels. Atorvastatin has been successful over the first generation of statins. Since its launch in the USA atorvastatin has reached sales in 1998, doubling from 1997, of $2.2 billion, capturing 38% of new prescriptions for cholesterol-lowering agents in the US and is now the most widely prescribed hypolipidaemic agent in the US (Warner-Lambert 1998 annual results).

An additional adverse event, reported for statins in general, is myopathy, defined as symptoms of muscle pain, tenderness and weakness, with creatinine kinase (CK) values >10 x Upper Limit of Normal (ULN). This adverse event is not considered to be dose related, and in addition the adverse events are potentially more serious, and consequently more problematical. In severe cases this can lead to rhabdomyolysis, which is a rare life threatening condition sometimes associated with renal failure. The incidence of raised CK levels (>10 x ULN - on 2 occasions at least 1 week apart with symptoms = myositis according to FDA) for statins has been reported as 3.1 per cent. (SmPC for atorvastatin). Myopathy and rhabdomyolysis have been particularly associated with taking a statin in combination with gemfibrozil, niacin, cyclosporin or erythromycin, (Hunninghake H. Et al. Current Opinion in Lipidolgy (1992), 3, 22-28) which are all substrates for P450 isoenzyme 3A4. The increase in adverse events associated with taking a combination of a statin drug with one of the other drugs mentioned above is probably due to a drug:drug interaction likely related to the metabolism of most statins also by the same cytochrome P450 isoenzyme 3A4. Therefore when a drug which is also metabolised by P450 3A4 is administered alongside a statin which also is metabolised by P450 3A4, the side effects discussed above are more likely to occur. Increase in the side effects, such as muscle damage, is thought to be due to elevated statin levels in muscle cells inhibiting farnesylation and geranylgeranylation of muscle proteins . Elevated levels of statins may be caused by any drug which affects P450 3A4. Therefore, currently on the labels of all commercially available statins the use of the statin in combination with drugs that are metabolised by P450 3A4 is not recommended and is contraindicated in certain cases.

Nearly all drugs are metabolised to some degree in the human, generally to a less lipid soluble compound which is more easily excreted by the kidney or in liver bile. The liver is the major site of drug metabolism and many drug metabolising enzymes occur at high concentration in the endoplasmic reticulum (which form microsomes upon homogenisation) of liver parenchymal cells (hepatocytes). Cytochrome P450 represents a major class of drug metabolising enzymes and exists as a family of isoenzymes found in hepatic microsomes. Six specific P450 isoenzymes are responsible for the metabolism of most of the commonly used

drugs, namely P450 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4.

A major disadvantage of the currently available "super statin" , atorvastatin, is that atorvastatin is metabolised by cytochrome P450 enzymes, in particular 3A4, which may cause drug interactions with other drugs which are inducers, inhibitors or substrates of the same P450 enzyme which metabolises atorvastatin. All of the first generation of statins are metabolised by P450 also. However, the rate of metabolism of pravastatin is sufficiently low that it is considered less susceptible to clinically relevant drug interactions. Therefore despite the lower efficacy of pravastatin, in its currently available doses, at reducing hypercholesterolaemia this is currently the statin of choice in combination with other drugs where the possibility of drug interactions is unacceptably high.

(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof (the calcium salt of which is disclosed in Figure 1 below), hereinafter referred to as the Agent, is also a statin and belongs to the class of what is now starting to be called a "superstatin".

The Agent is disclosed in European Patent Application, Publication No. 0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 as an inhibitor of HMG-CoA reductase which is a major rate-limiting enzyme in cholesterol biosynthesis. The Agent is described as useful in the treatment of hypercholesterolaemia, hyperlipoproteinaemia and atherosclerosis.

The Agent is not metabolised by cytochrome P450 3A4 and therefore does not possess the same potential for drug interaction shared with the currently available "super statin", i.e. atorvastatin, or any of the other currently available statins.

Therefore we present as a feature of the invention a non-interacting drug combination comprising a HMG CoA reductase inhibitor, which is the Agent, and a drug which is an inhibitor, inducer or substrate of P450 in particular, isoenzyme 3A4.

As a further feature of the invention we present use of a HMG CoA reductase inhibitor, which is the Agent, in the preparation of a medicament for use in combination therapy with a drug which is an inhibitor, inducer or substrate of P450, in particular, isoenzyme 3A4.

As a further feature of the invention we present use of a drug which is an inhibitor, inducer or substrate of P450, in particular, isoenzyme 3A4 in the preparation of a medicament for use in combination therapy with a HMG CoA reductase inhibitor, which is the Agent.

As a further feature of the invention we present a pharmaceutical formulation comprising the Agent, a drug which is an inducer, inhibitor or substrate of P450 isoenzyme 3A4 and a pharmaceutically-acceptable diluent, carrier or adjuvant.

As a further feature of the invention we present a pharmacy pack comprising a first drug which is the Agent and a second drug which is an inducer, inhibitor or substrate of P450 isoenzyme 4A4.

By the term "inducer of P450 " we mean a drug which increases the rate at which a P450 enzyme, in particular isoenzyme 3A4, metabolises a substrate, for example by increasing the activity of the P450 enzyme, decreasing the rate of biological inactivation of the P450 enzyme or by increasing the rate of transcription of the P450 gene.

By the term "inhibitor of P450" we mean a drug which lowers the rate at which a P450 enzyme, in particular isoenzyme 3A4, metabolises a substrate, for example by lowering the activity of the P450 enzyme or by lowering the rate of transcription of the P450 gene.

By the term "substrate of P450" we mean a drug which is metabolised by a P450 enzyme, in particular isoenzyme 3A4.

By the term "non-interacting drug combination" we mean a drug combination for which there is no adverse affect to the patient by its administration through the mechanism of drug metabolism by cytochrome P450 isoenzyme 3A4. It is recognised that in certain instances a

drug interaction may nevertheless occur between two such drugs when in combination through a completely different mechanism not involving drug metabolism, such as affecting drug absorption.

Whether a drug is an inhibitor, inducer or substrate of a P450 enzyme can be easily determined by procedures known to the skilled person. Such procedures may involve the exposure of a radiolabelled drug to hepatocytes or hepatocyte microsomes or isolated P450 enzyme and the use of analytic techniques, such as HPLC, in determining metabolite formation. A specific procedure is described herein.

By the term "combination" we mean either that the Agent and the drug of the combination are administered together in the same pharmaceutical formulation or that the Agent and the drug are administered separately. When administered separately components of the combination may be administered to the patient simultaneously or sequentially.

We have found that the Agent is not metabolised significantly by the major cytochrome P450 isoenzymes 1A2, 2C9, 2C19, 2D6 and 3A4. This is a further feature of the invention.

Preferred non-interacting combinations of the invention include those in which the Agent is combined with a drug which is also involved in lowering cholesterol and is also an inducer, inhibitor or substrate of P450 3A4. Examples include fibrates, such as bezafibrate, clofibrate, ciprofibrate, fenofibrate and gemfibrizol (preferably fenofibrate), and niacin. Specific embodiments of this preferred feature are described in Section B below.

Preferred non-interacting combinations of the invention include those in which the Agent is combined with a drug which is involved in treating cardiovascular conditions and which is also an inhibitor, inducer or substrate of P450 3A4. Examples include digitoxin, diltiazem, losartan, nifedipine, quinidine, verapamil and warfarin.

Preferred non-interacting combinations of the invention include those in which the Agent is combined with cyclosporin and /or tacrolimus (FK506) and therefore has utility in treating

elevated cholesterol levels in patients who are about to, or have recently undergone, a transplantation operation. Specific embodiments of this preferred feature are described below.

Preferred patients in which the combination of the invention is to be administered are those who suffer from myopathy or rhabdomylosis or who have already been found to suffer from myopathy or rhabdomylosis when treated with HMG Co A reductase inhibitor which is metabolised by P450 3A4, for example atorvastatin, simvastatin and lovastatin.

Other features of the invention include those described above wherein the Agent is used at doses of 5 to 80mg per day. When a dose range of 5 to 80 mg per day is referred to herein for the Agent other particular dosage ranges, which are further independent aspects of the invention, include (as appropriate) 10 to 80 mg per day, 10 to 60 mg per day, 10 to 40 mg per day, 5 to 40 mg per day, 5 to 20 mg per day, 10 to 20 mg per day, 20 to 60 mg per day, 20 to 40 mg per day and 40 to 60 mg per day. Particular dosages are 5, 10, 20, 40 and 80mg per day. A particularly suitable starting dose of the Agent in the methods referred herein is 5 to 10 mg per day, especially 10 mg per day.

P450 3A4 substrates include; acetominophen, aldrin, aflentanil, amiodorane, astemizole, benzphetamine, budenoside, carbamazepine, cyclophosphamide, cyclosporin, dapsone, digitoxin, ditiazem, diazepam, erthromycin, etoposide, flutamide, hydroxyarginine, ifosphamide, imipramine, lansoprazole, lidocaine, lovatidine, losartan, lovastatin, midrazolam, nifedipine, omeprazole, quinidine, rapamycin, retenoic acid, steroids, tacrolimus, teniposide, theophyline, toremifene, triazolam, troleandomycin, verapamil, warfarin, zatosetron and zonisamide.

P450 3A4 inhibitors include; clotrimazole, ethinylestradiol, gestodene, itraconazole, ketoconazole, miconazole, diltiazem, naringenin, erthromycin, cyclosporin and triacetyloleandomycin.

P450 3A4 inducers include; carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, sulfadimidine, sulfinipyrazone and triacetyloleandomycin.

Examples of other P450 inducers, inhibitors or substrates include those mentioned in Drug Metabolism Reviews (1997) Vol 29, Issue 1+2, pages 413-580, Rendic, S. and Di Carlo, F. J. "Human cytochrome P450 enzymes,: A status report summarising their reactions, substrates, inducers and inhibitors".

Dosages of the Agent may be administered according to the cholesterol lowering effect desired from a range of 5 to 80 mg per day in any number of unit dosages. Dosages of the drug which is an inducer, inhibitor or substrate of P450 3A4 are those which are advised for each drug, or which are commercially available. Advantageously, due to the lack of interaction at the level of P450 3A4, the skilled person may dose the Agent with a drug which is an inducer, inhibitor or substrate of P450 3A4 with out needing to make any adjustments.

The dose ranges and dosages described above are further independent features of the invention.

Preferably the Agent is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt (illustrated in figure 1).

Experimental

The experiment below is used to determine the in vitro metabolic fate of [^{14}C]- labelled Agent in human hepatocytes and, in addition, to determine the specific P450 isozymes involved in [^{14}C]- labelled Agent metabolism, if any. The latter experiment involves an investigation of the effects of P450 selective chemical inhibitors (see Table 1) on the metabolism of [^{14}C]-labelled Agent.

COMPOUND:	[^{14}C]- labelled Agent.
Chemical name:	Bis [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt
Isomer:	3*R*,5*S*,6*E* Stereoisomer
Molecular weight:	1001.16 (Ca salt)
Formulation ingredients:	The labelled Agent is dissolved in water to produce a solution suitable for addition to the incubates.

TISSUE SOURCE Human liver, suitable for the preparation of microsomes and hepatocytes, obtained from The International Institute for the Advancement of Medicine (Exton, USA). Human hepatocytes may, in addition, be obtained from Biowhittaker Ltd. or United Kingdom Human Tissue Bank (Leicester, England).

EXPERIMENTAL PROCEDURES

(1) METABOLISM OF [^{14}C]- LABELLED AGENT BY HUMAN HEPATOCYTES

[^{14}C]- labelled Agent (1 μM or higher concentration if required for analytical sensitivity) was incubated with hepatocytes in culture obtained from two human organ donors. Cultures were terminated with ethanol after 0, 6, 24 and 48 hours of incubation and stored at approximately -20°C until analysed. The metabolic competence of the hepatocytes was confirmed at the time of incubation by examining their ability to metabolise [^{14}C]-ethoxycoumarin (25 μM); aliquots were removed into methanol at the same time points as for the test compound.

Following incubation of [^{14}C]-ZD4522 with hepatocytes, metabolite profiles were generated by High Performance Liquid Chromatography (HPLC). The ability of hepatocytes to metabolise [^{14}C]-ethoxycoumarin was confirmed by HPLC.

ASSESSMENT OF DATA

Data generated was assessed with regard to the following:-

(1) Assess whether human hepatocytes metabolise [^{14}C]- labelled Agent.

(2) Quantitate the amount of each metabolite formed.

(2) ENZYMES INVOLVED IN METABOLISM OF THE AGENT

[^{14}C]- labelled Agent (at an appropriate concentration) was incubated with human hepatic microsomes in the absence and presence of selective P450 inhibitors (see Table 1). Similar incubations of [^{14}C]- labelled Agent with individual heterologously expressed P450 isoenzymes was also performed. Incubations were terminated by the addition of an appropriate organic solvent. Metabolite profiles of the incubates are generated by HPLC.

Table 1 Selective chemical inhibitors of P450 isozymes

P450 isozyme	Selective inhibitor
1A2	Furafylline
2C9	Sulphaphenazole
2C19	Omeprazole
2D6	Quinidine
3A4	Ketoconazole

ASSESSMENT OF DATA

Data generated during this study was assessed with regard to the following:-

(a) The rate and extent of metabolism of [^{14}C]- labelled Agent.

(b) The ability of the selective P450 inhibitors to decrease the metabolism of [^{14}C]- labelled Agent was compared in order to determine the isozyme(s) involved in the metabolism of [^{14}C]- labelled Agent.

The ability of individual expressed P450 isoforms to metabolise [^{14}C]- labelled Agent was assessed to aid determination of the P450 isozyme(s) involved in the metabolism of [^{14}C]- labelled Agent.

(c) These *in vitro* data can be used to predict the variability of the pharmacokinetics of the Agent in the population and the likely effects on the pharmacokinetics of the Agent during co-administration with known P450 enzyme inhibitors/inducers.

It was found that the Agent was not significantly metabolised by whole hepatocytes and that this was inhibited by sulphaphenazole and omeprazole.

FOR TREATING HYPERLIPIDAEMIA AND ASSOCIATED CONDITIONS IN POST TRANSPLANT PATIENTS RECEIVING IMMUNOSUPPRESSIVE THERAPY.

Two common drugs used in suppressing the human immune system, cyclosporin and tacrolimus (formerly called FK506), are known to be metabolised by cytochrome P450 3A4. In particular cyclosporin is also a known inhibitor of P450 3A4 and is therefore likely to reduce the metabolism of any other drug which is metabolised by P450 3A4.
Therefore where immunosuppressive therapy is prescribed, such as with the drugs cyclosporin and tacrolimus (especially cyclosporin), the attendant physician must be cautious as to any other therapy which may be jointly presented to the patient in combination.
Immunosuppressive therapy is most commonly used before, during and after human transplant operations. In particular with cardiac transplants the attendant physician may wish to also place the patient on statin drug therapy to reduce future incidents of coronary heart disease, stroke, peripheral arterial occlusive disease or peripheral vascular disease, particularly in patients with elevated cholesterol or in normolipidaemic patients with other risk factors associated with heart disease. In particular within this special patient group (human transplant patients), the patients are at high risk of developing accelerated atherosclerosis in the transplant organ in an aggressive fashion and within a short period of time due, in part, to the surgical damage to the blood vessels during transplantation, any previously underlying untreated conditions and the immunosupressive therapy. Hyperlipidaemia is common after transplantation even in patients who did not suffer hyperlipidaemia prior to transplantation, incidence 60-80% of recipients.

It is known that certain immunosuppresive drugs, such as steroids, cyclosporin and tacrolimus, raise cholesterol levels in patients (Wierzbicki AS (1999) IJCP 53 (1) 54-59). In addition cyclosporin and tacrolimus may raise the levels of fibrinogen and lipoprotein (a) in the patient, further accelerating the progression of atherosclerosis in the transplant patient (Hohaye H, Clin.Transplant (1997) 11, 225-230 and Hilbrands LB, J.Am.Soc.Nephrol (1995) 5, 2073-2081). This unusually accelerated atherosclerosis is present in about 20% of heart transplant patients at 1 year and 40-65% at 5 years (Chang G. Et al. American Heart Journal (1998), 136(2), 329-334). The incidence of accelerated atherosclerosis has been reported as causing a 1-18% incidence of CHD at one year and 20-50% incidence of CHD at 3 years in cardiac transplant patients (Erdoes LS, J.Vasc.Surg. (1995) 22, 434-440). Lovastatin, pravastatin and simvastatin have all shown to lower cholesterol levels in heart transplant patients. In a placebo controlled study pravastatin increased survival of transplant patients by 1 year and significantly reduced the incidence of haemodynamic organ rejection. Because of the lower incidence of serious drug interaction with the immunosuppresive therapy pravastatin is currently the statin drug of choice in post transplant treatment regimes. However, as discussed above, pravastatin does not lower lipid/cholesterol levels to such a great extent as, for example, atorvastatin.

We have discovered that the Agent is extremely effective at treating hypercholesterolaemia in patients following transplantation and that the Agent is not metabolised by cytochrome P450 isoenzyme 3A4. Therefore we have found through the use of the Agent in a clinical study that the Agent may be conveniently dosed to patients who are undertaking immunosuppressive therapy without any clinically significant side effects associated with the concomitant dosing of the Agent and the immunosuppressive drug(s) and, in addition, also achieve much higher levels of cholesterol lowering than has previously been achieved, such as by the use of pravastatin.

We present as the first feature of the invention a method of providing safe non-interacting cholesterol lowering therapy to a human patient undertaking immunosuppressive chemotherapy which method comprises administering to the patient the Agent.

Particular patients undertaking immunosuppressive chemotherapy who may benefit from the method of the invention are those who:

1) suffer primary (type IIa) hypercholesterolaemia (LDL-L ≥ 135 and TG<200);

2) suffer combined (type IIb) hypercholesterolaemia (LDL-C≥ 135 and TG≥200);

3) patients with established CHD or other atherosclerotic disease, such a PVD, stroke or peripheral arterial occlusive disease;

4) patients who are at high risk of developing CHD or other atherosclerotic disease, such as described above, because of a combination of risk factors. The term "high risk" is defined in the "Recommendations of Second Joint Task Force of European and other Societies on Coronary Prevention", (Wood, D. et. al. European Heart Journal, Atherosclerosis and Journal of Hypertension 1998) as absolute CHD risk of ≥ 20% over 10 years or will exceed 20% if projected to age 60 years. Whether a patient is at high risk or not may be determined by the charts which accompany the above recommendations and which charts are incorporated herein by reference. For example a male patient in his 40s who smokes and has a systolic blood pressure of 180 mm Hg or higher and a total plasma cholesterol concentration of 7 mmol/L or higher will be classified as high risk. Similarly other guidelines for reducing risk factors may be applied such as those described in;

a) JAMA, June 16, 1993-Vol 629, No.23, Pages 3015-3023 - "Summary of the NCEP Adult Treatment Panel II Report" - specifically Figure 1. Page 3018-3019 which is incorporated herein by reference.

b) Post Graduate Medical Journal 1993; 69(811): 359-369 - "Management of hyperlipidaemia: guidelines of the British Hyperlipidaemic Association"- specifically Table V and Table VI which are incorporated herein by reference.

c) Heart 1998; 80 Supplement 2:S1-S29 - "Joint British recommendations on prevention of coronary heart disease in clinical practice" - specifically Figure 1 on pages S4-S5, which is incorporated herein by reference.

d) The Lancet 1995; December 2, Vol.346, 1467-1471 - "Sheffield risk and treatment table for cholesterol lowering for primary prevention of coronary heart disease" - specifically the Table appearing at page 1468, which is incorporated herein by reference.

5) patients who suffer type I or II diabetes;

6) patients who are about to or have already undertaken a heart transplant;

The statin therapy may be administered so as to achieve in the patient undertaking immunosuppressive chemotherapy.

1) A reduction in the internal thickness of coronary artery atheroma of $\geq 30\%$ as measured by IVUS.

2) A reduction of LDL-C of at least 30, 40, 50%.

3) A maintenance or increase of HDL-C of at least 5, 10, 15%.

4) A change in any of the above values better than pravastatin at a similar dose and over the same period.

As a further feature of the invention, and due also to the fact that the Agent is not metabolised to any significant extent by P450 isoenzymes, it is possible to administer, more safely than before, to a patient receiving immunosuppresive therapy a fibrate and the Agent. As discussed earlier the administration of a fibrate and a statin has previously been associated with a higher incidence of rhabdomyolysis and myopathy. In addition fibrate drugs do interact with cyclosporin due to both being metabolised by the same P450 isoenzyme. Therefore, the use of

a statin and a fibrate drug in combination with immunosuppresive therapy was previously contraindicated due to the likelihood of possible serious interactions (Hunninghake 1992, Wanner C. Kidney Int. (1995) 52(suppl.), S60-S62; and Katznelson S. Contributions Nephrol. (1997) 120, 97-104). However, if possible, it would be advantageous to also administer a fibrate alongside a statin since fibrates are known to lower different lipoproteins than statins and therefore their combined pharmacology would be complementary in reducing even further the likelihood of CHD and other diseases mentioned above associated with the formation of atherosclerosis. Therefore the possibility of combining the Agent, which is not metabolised by P450 3A4, with a fibrate and an immunosuppresive therapy offers the additional possibility of lowering cholesterol to a greater extent in such patients than previously achieved and more safely than could previously be achieved by the administration of a statin, a fibrate and an immunosuppresive drug.

Fibrate drugs are thought to act through peroxisomal proliferating activator receptor-α (PPAR-α) and affect gene activation at a number of genes involved in atheroma. Patients on fibrate drugs show improved LDL subfraction distribution (reduced VLDL and raised HDL), reduced LDL and reduced triglyceride levels, and possible advantages through improving insulin sensitivity. Examples of fibrate drugs include, bezafibrate, ciprofibrate, fenofibrate and gemfibrozol.

By use of the term "safe non-interacting statin therapy" we mean that the Agent is not metabolised by P450 3A4 and therefore does not affect the metabolism of the immunosuppresive therapy or *vice versa*.

Diseases and conditions in which immunosuppressive therapy may be prescribed include, in addition to organ transplantation mentioned above, autoimmune diseases, including rheumatic disorders, such as, rheumatoid arthritis, osteoarthritis, lupus erthematosus; and other autoimmune disorders such as idiopathic thrombocytopenic purpura, autoimmune haemolytic anaemia and acute glomerulonephritis.

The agent may be administered at the same time as the immunosuppressive chemotherapy, or if not at the same time within a short time period of administration of the immunosuppressive therapy, such as in the same day, within 6, 3, 2 or 1 hour.

The Agent may be administered according to the cholesterol lowering effect desired from a range of 5-80 mg per day in any number of unit dosages, preferable once a day dosing. Ideal doses are 10, 20 and 40 mg once per day. Preferred doses are 20 and 40mg once per day.

Particular immunosuppressive drugs which may be combined with the Agents are those which are metabolised by liver enzymes, such as by P450 3A4, and therefore are not likely to have a drug interaction with the Agent. Examples include those described above, cyclosporin and tacrolimus, as well as corticosteroids, which are also metabolised in the liver. Examples of corticosteroids include prednisone (especially used for organ transplantation). Preferably at least one of the immunosuppressive agents, if more than one agent is used, is either cyclosporin or tacrolimus, preferably cyclosporin.

Example

The following non-limiting example is of a clinical trial to demonstrate the performance of this aspect of the invention.

PROTOCOL

Title:	A Double-blind, Parallel Group Study to Assess the Change in Coronary Artery Atheroma Burden Post Cardiac Transplantation as Measured via IVUS after 12 Months Dosing with the Agent versus Pravastatin
Objectives:	The primary objective of the study is to measure change in maximal mean intimal thickness of the anterior descending coronary artery as assessed by intravascular ultrasonography (IVUS) (read centrally) after 12 months of treatment with the Agent or pravastatin. A change from

baseline of ≥30% in intimal thickness is considered clinically significant.

The secondary objectives of the study are to measure the effects on coronary artery atheroma burden and to compare effects of the Agent with the following assessments:

- evidence of organ rejection as assessed by adverse event reports.
- measurement of LDL-C, HDL-C, apoB, apoA-I, Lp (a) concentrations, *ex vivo* platelet aggregation, fibrinogen, PAI-I, and the concentrations of circulating markers of vascular inflammation.
- comparison of lipid values after 52 weeks of treatment.
- measurement of inflammatory markers after 52 weeks of treatment (HLA antigen VCAM/ICAM expression as assessed by biopsy).
- to determine the drug's safety and tolerability.

Type and number of subjects: Approximately 40 men and women (aged 18 years and older) post cardiac transplant with hypercholesterolemia and triglycerides <400 mg/dl at the time of randomisation.

Trial treatment: Once daily doses of the Agent (10 mg) or pravastatin (10 mg) for two weeks, then titration of dose to 20 mg of the Agent or pravastatin 20 mg. After 4 weeks the dose should be titrated up to 40 mg of the Agent or 40 mg pravastatin. Patients who have had their dose titrated up to 40 mg may have their dose titrated down to 20 mg, at the discretion of the investigator.

Duration of treatment: Eligible subjects randomised to 1 of 2 treatment groups, the Agent or pravastatin, for 52 weeks.

Primary measure:	Mean change from baseline in maximal mean intimal thickness, as assessed by IVUS (read centrally).
Secondary measures:	Percent change from baseline in LDL-C at 6 and 12 months.
	Percent change from baseline in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, and triglycerides (TG).
	Percent change from baseline in ApoB, ApoB/ApoA-1, ApoA-1, Lp (a), and particle subfractions at 6 and 12 months.
	Percentage of subjects on each of the possible titrated doses at 12 months.
	Endocardial rejection will be considered an adverse event.
	Percent change from baseline in inflammatory markers (HLA antigen level and ICAM/VCAM expression).
	Safety evaluation as determined by adverse events, physical examination, and laboratory data.

TRIAL DESIGN

This is a multicenter, randomized, double-blind, parallel-group clinical trial. Within 1 to 4 weeks post surgery, subjects are randomized to receive either the Agent or pravastatin for 52 weeks. Subjects start treatment at a dose of 10 mg of either the Agent or pravastatin at Visit 2 and the dose is titrated to 20 mg at Visit 3 during the forced titration period. At Visit 4 and subsequent visits, the investigator has the option to increase each drug up to 40 mg during the optional titration period. Patients who have had their dose titrated up to 40 mg may have their dose titrated back down to 20 mg at the investigator's discretion.

TRIAL DESIGN

	Pre-transplant	Forced Titration		Optional Titration							
Visit	1	2	3	4	5	6	7	8	9	10	11
Week (W)/ Month (M)		W0	W2	W4	M2	M3	M4	M5	M6	M9	M12
Agent (mg)		10	20	≥ 20*							
PRAVASTATIN (mg)		10	20	≥ 20*							
		Randomisation**									

* Subjects who are tolerating 20 mg of the Agent or Pravastatin at Visit 4 may have their dose titrated up to 40 mg, at the discretion of the investigator.

** Subjects should be randomized within 4 weeks of cardiac transplantation and must not have received any other lipid lowering therapy post-surgery.

Inclusion criteria

(1) have undergone cardiac transplantation up to four weeks prior to randomization

(2) fasting TG concentrations of <4.52 mmol/L (400 mg/dl)

Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the trial:

(1) Use of other cholesterol lowering drugs or lipid lowering dietary supplements or food additives post-transplantation prior to entering the study

(2) history of serious or hypersensitivity reactions to other HMG-CoA reductase inhibitors

(3) pregnant women, women who are breast feeding, and women of child bearing potential who are not using chemical or mechanical contraception or have positive serum pregnancy test (a serum β-Human chorionic gonadotropin [β-HCG] analysis)

(4) Subjects with a history of diabetic ketoacidosis within the past 5 years are excluded.

(5) uncontrolled hypothyroidism defined as a thyroid stimulating hormone (TSH) >1.5 times the ULN at Visit 2 or subjects whose thyroid replacement therapy was initiated within the last three months

(6) use of concomitant medications as detailed below - except immune suppressants and diazepam

(7) current alcohol and/or drug abuse

(8) active liver disease or hepatic dysfunction as defined by elevations of $\geq$ 1.5 times the ULN at Visit 2 in any of the following liver function tests: ALT, AST, or bilirubin

(9) serum CK > 3 times ULN at Visit 2

(10) serum creatinine > 220 μmol/L (2.5 mg/dl)

(11) subjects with cancer or with a history of cancer who, in the opinion of the investigator, have more than a minimal chance of recurrence

(12) participation in another investigational drug trial less than 4 weeks before randomization into the trial

(13) subjects randomized to double-blind treatment who subsequently withdrew cannot re-enter this trial

(14) serious or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise the subject's safety or successful participation in the trial

(15) subjects taking cyclic hormone replacement therapy (HRT), cyclic oral contraceptive therapy (OCT), a depot progesterone injection, or subjects whose non-cyclic HRT or OCT was initiated within the last 3 months

DISALLOWED MEDICATIONS

CLASS OF DRUG	GENERIC NAME
Antibiotics/ antifungals	Erythromycin Base Erythromycin Ethyl Succinate, Acetyl Sulfisoxazole Rifampicin Fluconazole Ketaconazole Itraconzole
Anti-epileptics/ antidepressants	Phenytoin Phenobarbitol Fluoxetine Carbemazepine
Acne treatment	Isotretinoin
Antiulcer drugs	Cimetidine Cisapride

CLASS OF DRUG	GENERIC NAME
Systemic Steroids	Triamcinolone Acetonide Triamcinolone Diacetate Betamethasone Sodium Phosphate Betamethasone Acetate Hydrocortisone Hydrocortisone Acetate Hydrocortisone Sodium Phosphate Hydrocortisone Sodium Succinate Cortisone Acetate Dexamethasone Dexamethasone Acetate Dexamethasone Sodium Prednisone Methylprednisolone Methylprenisolone Acetate Methylprednisolone Sodium Succinate Prednisolone Tebutate Prednisolone Sodium Phosphate Methyltestosterone Fluoxymesterone
Antihistamine	Astemizole Terfenadine

CLASS OF DRUG	GENERIC NAME
Lipid Regulation	Niacin/Nicotinic Acid Probucol Psyllium Preparations Clofibrate Cholestyramine Colestipol Hydrochloride Gemfibrozil Atorvastatin Lovastatin Pravastatin (except study medication) Simvastatin Fluvastatin Cerevestatin Fish oils (any dose) lipid lowering dietary supplements lipid lowering food additives
Hormone Therapy	Estrogen and progesterone combinations which are bi or tri phasic.

Friedewald Equation

The LDL-C level is calculated from the Friedewald equation as follows:

For SI units (mmol/l)

LDL-C = Total cholesterol - [HDL-C + Triglycerides/2.2)

For non-SI units (mg/dl):

LDL-C = Total cholesterol - [HDL-C + triglycerides/5]

Summary of NCEP Goals for Lipid Management[a]

NCEP Risk Category	Target LDL-C (NCEP)
No CHD/PVD and 1 or no risk factors	< 160 mg/dL
No CHD/PVD and 2 or more risk factors	< 130 mg/dL
Clinically evident CHD/PVD	≤ 100 mg/dL

[a] Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Bethesda (MD): National Institutes of Health, National Heart and Lung Institute 1993 Sep Report No.: 93-3095.
NCEP National Cholesterol Education Program.

FOR TREATING HYPERLIPIDAEMIA, AND ASSOCIATED CONDITIONS, USING A COMBINATION OF THE AGENT AND A FIBRATE DRUG OR NIACIN

Myopathy and rhabdomyolysis have been associated with taking a statin in combination with gemfibrozil, niacin, cyclosporin or erythromycin, (HMG CoA reductase inhibitors, Hunninghake, Current Opinion in Lipidology (1992) 3, 22-28) which are all substrates for P450 3A4. Additionally, adverse events associated with taking a fibrate drug have also been reported to increase with concomitant statin therapy, such as a myosistis-flu like syndrome, which occasionally occurs in patients receiving gemfibrozil, increases to 5% of patients when a statin is also administered.

Combination of a statin with a fibrate drug is contraindicated on the labels, both in the USA and Europe, of all commercially available statins. Despite the possibility of the occurrence of serious drug interactions doctors do prescribe combination therapy of a statin and a fibrate drug to patients with more severe levels of hypercholesterolaemia, such as in patients with

familial combined hyperlipidaemia, where the risk of a serious drug interaction is outweighed by the benefits of the combination therapy. It is recommended that where combination therapy of a fibrate drug and a statin is prescribed that patients should have their CK value determined on a regular basis, typically every 6-weeks, until a stable pattern is established. Therapy is stopped if muscle symptoms occur in association with elevated CK activity. However, as quoted from the US label of Lipitor™ "there is no assurance that such monitoring [of CK levels] will prevent the occurrence of severe myopathy".

We have discovered that the Agent is extremely effective at treating mixed hyperlipidaemia and hypertriglyceridaemia in patients when combined with a fibrate drug and that the Agent is not metabolised by cytochrome P450 isoenzyme 3A4. Therefore we have found through the use of the Agent in a clinical study that the Agent may be conveniently dosed to patients who are also taking a fibrate drug without any clinically significant side effects associated with the concomitant dosing of the Agent and the fibrate drug. In addition much higher levels of lipid lowering than has previously been achieved can be achieved by the use of the Agent and a fibrate drug. The combination is of most use in mixed hyperlipidemia where the LDL and VLDL and TGs are all elevated.

We present as the first feature of the invention a method of providing safe non-interacting lipid lowering combination therapy to a mammal, including a human patient, preferably a patient suffering mixed hyperlipidaemia and hypertriglyceridaemia, which method comprises administering to the patient the Agent and a fibrate drug or niacin.

By the term "combination" as used herein we mean either (1) that the Agent and the fibrate drug of the combination are administered together in the same pharmaceutical formulation or (2) that the Agent and the drug are administered separately. When administered separately components of the combination may be administered to the patient simultaneously or sequentially.

By the term "fibrate drug" we mean the class of drugs which are based around the structure/activity of fibric acid and such drugs include the following commercially available

versions; bezafibrate, clofibrate, ciprofibrate, fenofibrate and gemfibrizol, preferably fenofibrate.

Preferred patients in which the combination of the invention is to be administered are those who have already been found to suffer from myopathy or rhabdomylosis when treated with a statin and/or with a fibrate drug which is metabolised by P450 3A4.

Particular patients who may benefit from the method of the invention are those who:

1) suffer combined (type IIb) hypercholesterolaemia (typically LDL-C≥ 135 mg/dL and TG≥200 mg/dL);

2) suffer familial (type IV and V) hypercholesterolaemia;

3) patients suffering secondary hypercholesterolaemia from such conditions as:

a) diabetes (type I or II),

b) nephrotic syndrome,

c) uremia,

d) hyperthyroidism, and

e) obstructive liver disease.

4) patients with established CHD or other atherosclerotic disease, such a PVD, stroke or peripheral arterial occlusive disease;

5) patients who are at high risk of developing CHD or other atherosclerotic disease, such as described above, because of a combination of risk factors. The term "high risk" is defined in the "Recommendations of Second Joint Task Force of European and other Societies on Coronary Prevention", (Wood, D. et. al. European Heart Journal, Atherosclerosis and Journal of Hypertension 1998) as absolute CHD risk of ≥ 20% over 10 years or will exceed 20% if projected to age 60 years. Whether a patient is at high risk or not may be determined by the charts which accompany the above recommendations and which charts are incorporated herein by reference. For example a male patient in his 40s who smokes and has a systolic blood pressure of 180 mm Hg or higher and a total plasma cholesterol concentration of 7 mmol/L or higher will be classified as high risk. Similarly other guidelines for reducing risk factors may be applied such as those described in;

a) JAMA, June 16, 1993-Vol 629, No.23, Pages 3015-3023 - "Summary of the NCEP Adult Treatment Panel II Report" - specifically Figure 1. Page 3018-3019, which is incorporated herein by reference.

b) Post Graduate Medical Journal 1993; 69(811): 359-369 - "Management of hyperlipidaemia: guidelines of the British Hyperlipidaemic Association"- specifically Table V and Table VI, which are incorporated herein by reference.

c) Heart 1998; 80 Supplement 2:S1-S29 - "Joint British recommendations on prevention of coronary heart disease in clinical practice" - specifically Figure 1 on pages S4-S5, which is incorporated herein by reference.

d) The Lancet 1995; December 2, Vol.346, 1467-1471 - "Sheffield risk and treatment table for cholesterol lowering for primary prevention of coronary heart disease" - specifically the Table appearing at page 1468, which is incorporated herein by reference.

The statin therapy may be administered so as to achieve in the patient receiving a fibrate drug or niacin:

1) a reduction of LDL-C of at least 30, 40, 50, 60, 70 or 80%.
2) a maintenance or increase of HDL-C of at least 5, 10, 15%.
3) a reduction in triglycerides of at least 10, 20, 30 or 40%.

The combination of the fibrate, or niacin, and the Agent may be applied as separate dosage forms, which may be taken simultaneously or sequentially, or in a combined dosage form. The combination of the fibrate and the Agent will also have an additive or synergistic effect on the reduction in LDL-C, maintenance or increase of HDL-C or reduction in triglyceride in the patients blood.

In addition the combination of niacin and the Agent may be applied as separate dosage forms, which may be taken simultaneously or sequentially, or in a combined dosage form. The combination of the fibrate and the Agent will also have an additive or synergistic effect on

the reduction in LDL-C, maintenance or increase of HDL-C or reduction in triglyceride in the patients blood.

Doses of the Agent which are administered are at the discretion of the attendant physician generally taking into account the severity of the disease, the age, weight and sex of the patient. However typical doses will be from 5 to 80 mg per day orally, preferably as a once a day oral tablet form.

Doses of the fibrate drug or niacin which are administered in the combination of the invention also are at the discretion of the attendant physician taking into account all of the above factors plus in particular which drug is used.

For clofibrate (such as Atromid-S®) 20-30 mg/kg body weight daily in 2 or 3 divided oral doses after meals is typical.

For bezofibrate (such as Bezalip®) 400 mg once a day orally, after food at night or in the morning, is typical.

For fenofibrate (such as Lipantil®) 200 mg once a day, or 62 mg three times a day, with food is typical.

For gemfibrozil (such as Lopid®) 600 mg twice a day orally is typical.

For cipofibrate (such as Modalim®) 100 mg once a day orally is typical.

For niacin (NIASPAN®, an extended release niacin formulation, and preferred feature) 500mg once to four times daily, preferably twice or four times daily.

A preferred fibrate drug is fenofibrate.

Preferably the AGENT is administered to a patient receining niacin at 10mg or 40mg daily doses.

The particular aspect of this invention is illustrated by the following non-limiting examples:

Clinical Trial

A Randomised, Non-controlled, Single-centre, Open-label, 3-way Crossover Trial to Assess the Effect of Co-administration of the Agent and Fenofibrate on the Pharmacokinetics of Each Compound in Healthy Male Volunteers

Objectives:	The primary objective of this trial is to assess the effect of co-administration of the Agent and fenofibrate on the pharmacokinetics of both the Agent and fenofibrate The safety of all volunteers will be ensured by clinical monitoring
Type and number of volunteers:	14 healthy male volunteers
Trial design:	The trial will be a randomised, non-controlled, 3-way crossover study carried out at a single centre
Trial treatment:	This trial will consist of three 7-day treatment periods (Periods A, B, and C). Volunteers will receive, in random order, a 10 mg capsule of the Agent once daily for 7 days, a 67 mg fenofibrate capsule 3 times daily for 7 days and the combination for 7 days. There will be a minimum of a 3-week washout between each trial period.
Duration of treatment:	The study will consist of 3 periods of 7-day dosing (a total of 21 dosing days) with a 3-week washout between dosing in Periods A, B and C.
Primary endpoints:	The primary endpoints are: • AUC(0-24) and C_{max} of the Agent in the presence and absence of fenofibrate • AUC(0-8) and C_{max} of fenofibrate in the presence and absence of the Agent

Secondary endpoints:

the secondary endpoints are:

- t_{max}, $t_{1/2}$, C_{min} for the Agent in the presence and absence of fenofibrate
- t_{max}, $t_{1/2}$, C_{min} for fenofibrate in the presence and absence of the Agent
- safety assessments: symptoms, blood pressure and pulse rate, ECG, clinical chemistry, haematology and urinalysis

TRIAL PLAN

Summary of procedures - overall plan for Trial Periods A, B and C

Trial Days	Medical	Doses of the Agent / fenofibrate or combination	P & BP	12 lead ECG	Safety Blood & Urine	Kinetics of the Agent	Kinetics Fenofibrate
Pre-trial	+		+	+	+[a]		
-1					+[b]		
1		+				+[c]	+[c]
2		+			+[b]	+[d]	+[e]
3		+				+[d]	+[e]
4		+			+[b]		
5		+					
6		+			+[b]	+[d]	+[e]
7		+	+	+		+[d]	+[e]
8					+[b]	+[d]	
9						+[d]	
10					+[b]	+[d]	
Post-trial	+		+	+	+[a]	+[d]	

[a]Full clinical chemistry, haematology and urine labstix.

[b]Clinical chemistry only: urea, creatinine, total protein, albumin, uric acid, total bilirubin (and unconjugated and conjugated bilirubin if total bilirubin raised), alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotranseferase (AST), gamma glutamyltransferase, creatine kinase (CK), sodium, potassium, calcium, cholesterol and triglycerides.

[c] Pre-dose all trial periods.

[d]Only trial periods when volunteers receive the Agent

eonly trial periods when volunteers receive fenofibrate

P = pulse; BP = blood pressure

TRIAL PLAN II

Trial Day 7 in Periods A, B and C

Time	P & BP (L)	12 lead ECG	Safety blood & urine [c]	Kinetics of the Agent [b]	Kinetics fenofibrate[c]	Meals & Fluids
Pre-dose	+	+		+	+	B
Dose (0 h)						D
0.5 h				+	+	
1 h				+	+	
2 h				+	+	D
3 h	+	+		+	+	
4 h				+	+	M, F
5 h	+	+		+	+	
6 h				+	+	
8 h				+	+	S
10 h				+		M
12 h	+	+		+		F
14 h						S
18 h				+		W
24 h	+	+	+[a]	+		
30 h				+		
48 h				+		
54 h				+		
72 h			+[a]	+		

[a]clinical chemistry only: urea, creatinine, total protein, albumin, uric acid, total bilirubin (and unconjugated and conjugated bilirubin if total bilirubin raised), alkaline phosphatase, ALT, AST, gamma glutamyltransferase, CK, sodium, potassium, calcium, cholesterol and triglycerides.

[b]Only trial periods when volunteers receive the Agent

[c]Only trial periods when volunteers receive fenofibrate

L = lying; P = pulse; BP = blood pressure; D = drink; S = snack; M = meal; F = free access to permitted fluid and food; W = free access to water only

1 OBJECTIVES

Primary objective

The primary objective of this trial is to assess the effect of co-administration of the Agent and fenofibrate on the pharmacokinetics of both the Agent and fenofibrate.

Secondary objective

There is no secondary objective for this trial.

The safety of all volunteers will be ensured by clinical monitoring.

Design

The trial will be a randomised, non-controlled, open-label, 3-way crossover study carried out at a single centre.

Volunteers will receive 3 treatment regimens in random order:

- 10 mg of the Agent once daily for 7 days
- fenofibrate (Lipantil™) 67 mg x 3 daily for 7 days
- the Agent (10 mg once daily) and fenofibrate (Lipantil™, 67 mg x 3 daily) given in combination for 7 days

There will be a minimum of 3 weeks (21 days) washout between each treatment period.

Inclusion criteria

For inclusion in the trial, volunteers must meet all of the following criteria:

- male, aged between 18 and 65 years inclusive
- normal clinical examination, including medical history, resting electrocardiogram (ECG) and 24-hour continuous ambulatory ECG (if not performed in the past 12 months)
- negative screens for serum hepatitis B surface antigen and hepatitis C antibody and a normal screen for ferritin within the previous 12 months
- weight not differing by more than 20% from the desirable weight (Metropolitan Height and Weight Tables)

Exclusion criteria

Volunteers must be excluded from the trial if any of the following criteria are met:

- use of any medication or therapy, including drugs of abuse
- receipt of another new chemical entity in the 4 months before dosing in this trial (a new chemical entity is defined as a compound which has not been submitted for marketing authorisation)
- participation in another trial within 3 months before the start of the present trial, apart from non-invasive methodology trials in which no drugs were given
- any acute illness within 2 weeks before the start of the trial
- any clinically significant abnormalities in clinical chemistry, haematology or urinalysis results. In addition the following clinical chemistry parameters should be no greater than the upper limit of normal: total bilirubin, ALT, AST and CK
- risk (in the investigator's opinion) of transmitting, through blood or other body fluids, the agents responsible for acquired immune deficiency syndrome (AIDS), hepatitis B or hepatitis C
- definite or suspected personal history or family history of adverse drug reactions, or hypersensitivity to drugs with a similar chemical structure to the Agent or related statins, or fenofibrate and related fibrate drugs
- history or presence of gastrointestinal, hepatic, biliary or renal disease or other condition known to interfere with absorption, distribution, metabolism or excretion of drugs
- history of Gilbert's syndrome
- if participation in the trial would result in the volunteer donating more than 1350 ml of blood in the 12 months before the end of the trial
- excessive intake of alcohol, defined as a maximum weekly intake of greater than 28 units (1 unit equals half a pint of beer or a measure of spirits)

- treatment in the previous 3 months with any drug known to have a well-defined potential for hepatotoxicity (eg, halothane)
- clinical judgement by the investigator or the volunteer's general practitioner that the volunteer should not participate in the trial

Volunteer restrictions

Volunteers will be required to:

- abstain from taking any medication (including over-the-counter remedies) from 96 hours before Trial Day 1 to 72 hours after receiving the last dose of the Agent or morning dose of fenofibrate in each trial period unless the investigator has given prior consent
- fast from midnight on the night before each trial day and eat a light breakfast on arrival on Trial Day 1 to 7 in each trial period
- refrain from driving, cycling, using machinery (drills, sanders, sharp instruments etc.) for 24 hours after receiving first dose on Trial Day 7 in each period
- remain for 24 hours after receiving first dose on Trial Day 7 in each trial period
- abstain from smoking, consuming grapefruit, grapefruit juice, liquorice or caffeine-containing drinks or foods (eg, coffee, tea, cocoa, chocolate and cola) from midnight before Trial Day 1 until 72 hours after receiving the last dose of the Agent or morning dose of fenofibrate in each trial period
- abstain from drinking alcohol from 96 hours before Trial Day 1 until 72 hours after receiving the last dose of the Agent or morning dose fenofibrate in each trial period
- refrain from physical exercise from 96 hours before Trial Day 1 until 72 hours after receiving the last of the Agent or morning dose of fenofibrate in each trial period
- refrain from potentially hazardous work or activities, from receiving the first dose of the Agent or fenofibrate until the post-trial medical

- abstain from donating blood during the trial and for 3 months following their last dose of trial treatment

Formulation, presentation and storage

Dosage and administration

Capsules of the Agent or fenofibrate will be taken orally with 200 ml of purified water with the volunteer sitting in an upright position.

On Trial Days 1 to 7 of each treatment period, volunteers will receive one of the following treatments:

- 1 x 10 mg capsule of the Agent to be taken between 08:30 and 09:30 hours
- 3 x 67 mg fenofibrate capsules
  - the 1st capsule to be taken between 08:30 and 09:30 hours
  - the 2nd capsule to be taken between 16:30 and 17:30 hours with food
  - the 3rd capsule to be taken between 22:30 and 23:30 hours with food-
- 1 x 10 mg capsule of the Agnet and 3 x 67 mg fenofibrate capsules:
  - 1 capsule of the Agent and the 1st fenofibrate capsule to be taken simultaneously between 08:30 and 09:30 hours
  - the 2nd fenofibrate capsule to be taken between 16:30 and 17:30 hours with food
  - the 3rd fenofibrate capsule to be taken between 22:30 and 23:30 hours with food

On Trial Days 1 to 6 of each trial period, volunteers will visit the unit daily and will be allowed to leave the unit immediately after administration of doses of the Agent, fenofibrate or the the Agent / fenofibrate combination, except on Trial Day 7 when volunteers will remain resident for 24 hours.

In trial periods when the volunteers are randomised to fenofibrate, they will take the further 2 doses of fenofibrate at home. The volunteers will be provided with 1 pot of fenofibrate to be

taken as outlined above. Volunteers will be issued with a pre-set timer to ensure that the dose is taken at the correct time, and a diary card to document the dose was taken.

When the the Agent and fenofibrate are given to the volunteers, the tear-off labels will be attached to the appropriate case report form (CRF). The investigator must ensure that each volunteer receives the correct treatment.

Clinical and laboratory assessments

Primary endpoints

The following parameters will be measured as primary endpoints:

- AUC(0-24) and C_{max} of the Agent in the presence and absence of fenofibrate
- AUC(0-8) and C_{max} of fenofibrate in the presence and absence of the Agent

Secondary endpoints

The following parameters will be measured as secondary endpoints:

- t_{max}, $t_{1/2}$, C_{min} for the Agent in the presence and absence of fenofibrate
- t_{max}, $t_{1/2}$ and C_{min} for fenofibrate in the presence and absence of the Agent

safety assessments: symptoms, blood pressure and pulse rate, ECG, clinical chemistry, haematology and urinalysis.

Pharmaceutical compositions

The following Example illustrates, but is not intended to limit, pharmaceutical dosage forms which are suitable for use in the invention as defined herein:

Capsule	mg
The Agent	5.0
Lactose	42.5
Cornstarch	20.0
Microcrystalline cellulose	32.0
Pregelatinised starch	3.3

Hydrotalcite	1.1
magnesium stearate	1.1

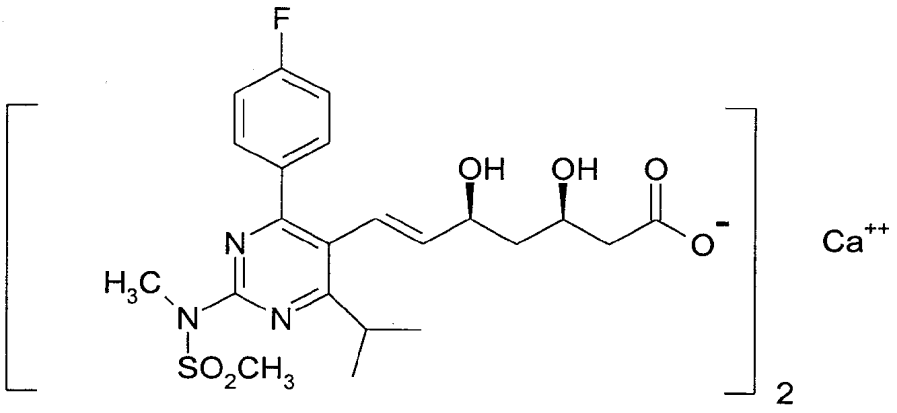
Capsules containing 1, 2.5 or 10mg of the Agent may be obtained similarly using more or less lactose as appropriate, to maintain a total fill weight of 105mg.

ABBREVIATIONS AND CONVENTIONS USED

Abbreviation	Term
ALT	alanine aminotransferase
ALP	alkaline phosphatase
apo B	apolipoprotein B 100
AST	aspartate aminotransferase
AUC	area under the concentration curve from zero to infinity
AUC(0-t)	area under the curve of plasma concentration against time from zero to time of last quantifiable concentration
CABG	Coronary artery bypass graft
C_{max}	maximum concentration
CK	creatinine kinase
CVA	cerebrovascular accident
ECG	electrocardiogram
EAS	European Atherosclerosis Society
EDTA	ethylenediamine-tetraacetic acid
XGT	Gemma glutaryl transferase
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A

Abbreviation	Term
HDL	high-density lipoprotein
HPLC	high-performance liquid chromatography
HRT	hormone replacement therapy
IU	International Units
IVUS	Intravascular ultrasenography
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
MVA	mevalonic acid
NC	not calculable
NCEP	national cholesterol eduction program
NDSR	national data system for research
THC	tetrahydrocannabinol
TG	triglyceride
$t_{½}$	terminal elimination half-life
t_{max}	time of maximum concentration
TC	total cholesterol
TG	triglycerides
TIA	transient ischemic attack
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VLDL	very low-density lipoprotein

Figure 1



Formula I

Claims

1. A non-interacting drug combination comprising a HMG-CoA reductase inhibitor, which is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof and a drug which is an inhibitor, inducer or substrate of P450 isoenzyme 3A4.

2. A non-interacting drug combination, as claimed in claim 1, wherein the second drug is an inhibitor or inducer of P450 isoenzyme 3A4.

3. A non-interacting drug combination, as claimed in either claim 1 or claim 2, wherein each drug is administered together or each drug is administered sequentially.

4. A non-interacting drug combination, as claimed in any claim from 1 to 3, wherein the second drug is used to lower cholesterol and is an inducer, inhibitor or substrate of P450 isoenzyme 3A4.

5. A non-interacting drug combination, as claimed in claim 4, wherein the second drug is selected from bezafibrate, clofibrate, fenofibrate, gemfibrozol and niacin.

6. A non-interacting drug combination, as claimed in claim 5, wherein the second drug is fenofibrate.

7. A non-interacting drug combination, as claimed in any claim from 1 to 3, wherein the second drug is used in treating cardiovascular conditions and is also an inhibitor, inducer or substrate of P450 isoenzyme 3A4.

8. A non-interacting drug combination, as claimed in claim 7, wherein the second drug is selected from digitoxin, diltiazem, losartan, nifedipine, quinidine, verapamil and warfarin.

9. A non-interacting drug combination, as claimed in any claim from 1 to 3, wherein the second drug is used in immunosuppresion therapy and is an inducer, inhibitor or substrate of P450 isoenzyme 3A4.

10. A non-interacting drug combination, as claimed in claim 9, wherein the second drug is selected from cyclosporin, tacrolimus and a corticosteroid.

11. A non-interacting drug combination, as claimed in any claim from 1 to 10, wherein (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof is dosed at 5, 10, 20, 40 or 80mg once per day.

12. A pharmaceutical formulation comprising (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof, a drug which is an inducer, inhibitor or substrate of P450 isoenzyme 3A4 and a pharmaceutically-acceptable diluent, carrier or adjuvant.

13. A pharmaceutical formulation, as claimed in claim 12, wherein the second drug is a substrate of P450 isoenzyme 3A4 and is selected from acetominophen, aldrin, aflentanil, amiodorane, astemizole, benzphetamine, budenoside, carbamazepine, cyclophosphamide, cyclosporin, dapsone, digitoxin, ditiazem, diazepam, erthromycin, etoposide, flutamide, hydroxyarginine, ifosphamide, imipramine, lansoprazole, lidocaine, lovatidine, losartan, lovastatin, midrazolam, nifedipine, omeprazole, quinidine, rapamycin, retenoic acid, steroids, tacrolimus, teniposide, theophyline, toremifene, triazolam, troleandomycin, verapamil, warfarin, zatosetron and zonisamide.

14. A pharmaceutical formulation, as claimed in claim 12, wherein the second drug is an inhibitor of P450 isoenzyme 3A4 and is selected from clotrimazole, ethinylestradiol, gestodene, itraconazole, ketoconazole, miconazole, diltiazem, naringenin, erthromycin, cyclosporin and triacetyloleandomycin.

15. A pharmaceutical formulation, as claimed in claim 12, wherein the second drug is an inducer of P450 isoenzyme 3A4 is selected carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, sulfadimidine, sulfinipyrazone and triacetyloleandomycin.

16. A pharmacy pack comprising a first drug which is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof and a second drug which is an inducer, inhibitor or substrate of P450 isoenzyme 4A4.

17. A pharmacy pack, as claimed in claim 16, wherein the second drug is used to lower cholesterol and is an inducer, inhibitor or substrate of P450 isoenzyme 3A4.

18. A pharmacy pack, as claimed in claim 17, wherein the second drug is selected from bezafibrate, clofibrate, fenofibrate, gemfibrozol and niacin.

19. A pharmacy pack, as claimed in claim 16, wherein the second drug is used in treating cardiovascular conditions and is also an inhibitor, inducer or substrate of P450 isoenzyme 3A4.

20. A pharmacy pack, as claimed in claim 19, wherein the second drug is selected from, digitoxin, diltiazem, losartan, nifedipine, quinidine, verapimil and warfarin.

21. A pharmacy pack, as claimed in claim 16, wherein the second drug is a substrate of P450 isoenzyme 3A4 and is selected from acetominophen, aldrin, aflentanil, amiodorane, astemizole, benzphetamine, budenoside, carbamazepine, cyclophosphamide, cyclosporin, dapsone, digitoxin, ditiazem, diazepam, erthromycin, etoposide, flutamide, hydroxyarginine, ifosphamide, imipramine, lansoprazole, lidocaine, lovatidine, losartan, lovastatin, midrazolam, nifedipine, omeprazole, quinidine, rapamycin, retenoic acid, steroids, tacrolimus, teniposide, theophyline, toremifene, triazolam, troleandomycin, verapamil, warfarin, zatosetron and zonisamide.

22. A pharmacy pack, as claimed in claim 16, wherein the second drug is an inhibitor of P450 isoenzyme 3A4 and is selected from clotrimazole, ethinylestradiol, gestodene, itraconazole, ketoconazole, miconazole, diltiazem, naringenin, erthromycin, cyclosporin and triacetyloleandomycin.

23. A pharmacy pack, as claimed in claim 16, wherein the second drug is an inhibitor of P450 isoenzyme 3A4 and is selected from carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, sulfadimidine, sulfinipyrazone and triacetyloleandomycin.

24. Use of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in combination therapy with a second drug which is an inducer, inhibitor or substrate of P450 isoenzyme 3A4.

25. Use of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in cholesterol lowering therapy in combination therapy with a second drug which is an inducer, inhibitor or substrate of P450 isoenzyme 3A4.

26. Use, as claimed in claim 25, wherein the second drug is selected from bezafibrate, clofibrate, fenofibrate, gemfibrazol and niacin.

27. Use of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in the treatment of cardiovascular condition in combination with a second which is an inducer, inhibitor or substrate of P450 isoenzyme 3A4.

28. Use, as claimed in claim 27, wherein the second drug is selected from digitoxin, diltiazam, losartan, nifedipine, quinidine, verapimil and warfarin.

29. Use of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in cholesterol lowering therapy in a patient receiving immunosuppresive therapy.

30. Use, as claimed in claim 29, wherein the immunosuppresive therapy comprises the administration of a drug selected from cyclosporin, tacrolimus and a corticosteroid.

31. Use of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in cholesterol lowering therapy in combination with a second drug which is selected from bezafibrate, clofibrate, fenofibrate, gemfibrazol and niacin in a patient receiving immunosuppresive therapy.

32 Use as claimed in claim 31 wherein the immunosuppressive therapy comprises the administration of a drug selected from cyclosporin, tacrolimus and a corticosteroid.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/00278

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 521 417 A (SHIONOGI SEIYAKU KABUSHIKI KAISHA) 7 January 1993 (1993-01-07) cited in the application page 2, line 1 - line 29 examples 1,7 claims 1-9	24

☐ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 May 2000	05/06/2000

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INTERNATIONAL SEARCH REPORT

Information on patent family members

I ıational Application No
PCT/GB 00/00278

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		TR 27627 A	14-06-1995

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/445, 31/44 — A1

(11) International Publication Number: **WO 00/69438**

(43) International Publication Date: 23 November 2000 (23.11.00)

(21) International Application Number: PCT/GB00/01775

(22) International Filing Date: 9 May 2000 (09.05.00)

(30) Priority Data:
9911017.3 13 May 1999 (13.05.99) GB

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(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHARMACEUTICAL COMBINATION OF NEUROKININ RECEPTOR ANTAGONIST AND PROTON PUMP INHIBITOR

(57) Abstract

A combination comprising an NK–1 antagonist and an agent capable of reducing the pH of gastric juice in the gut, and pharmaceutical compositions containing the combination, and methods of using the combination for treating various diseases.

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PHARMACEUTICAL COMBINATION OF NEUROKININ RECEPTOR ANTAGONIST AND PROTON PUMP INHIBITOR

Field of the Invention

The present invention relates to novel combinations comprising an NK-1 antagonist and an agent capable of reducing the pH of gastric juice in the gut. Furthermore, the invention relates to pharmaceutical compositions comprising such combinations and the use of such combinations and compositions in the treatment of diseases related to the gastrointestinal system.

Background

It is known in the art that proton pump inhibitors and H_2 antagonists may be used to decrease the pH of the gastric juice in the gut. However, neither of these prevent the relaxation of the lower esophageal sphincter. Additionally, prolonged administration of these compounds may be deleterious or give rise to side effects in certain patients. For example, the prolonged administration of a proton pump inhibitor in some cases leads to abdominal pain, asthenia, constipation, dizziness, or rash.

Substance P is the physiological agent that induces, at least in part, relaxation of the lower esophageal sphincter. NK-1 antagonists are known to block the activity of substance P, thereby blocking the relaxation of the this sphincter. While blocking relaxation of the sphincter can reduce the severity of acid reflux, it does not prevent the aspiration of the acid, which can lead to gastric asthma.

While various investigators have studied the use of NK-1 antagonists, H_2 antagonists, and proton pump inhibitors independently in such conditions as GERD and gastric asthma, none have proposed the combination therapy provided by the present invention. The present invention relates to a combination of an NK-1 antagonist, an H_2 antagonist, and/or a proton pump inhibitor that work in concert to provide relief for those who suffer from gastric asthma, GERD, and related conditions.

Summary of the Invention

The present invention relates to pharmaceutical compositions, and in particular to pharmaceutical compositions containing a neurokinin-1 (NK-1) antagonist and a proton pump inhibitor, which are useful in the prevention and treatment of diseases brought about by hypersecretion of gastric acid in the gut and/or relaxation of the lower esophageal sphincter, such as gastric asthma and gastroesophageal reflux disease (GERD). During reflux episodes in

patients with GERD, acid may be aspirated into the lower esophagus, causing esophagitis. GERD or hyper-relaxation of the lower esophageal sphincter can also allow acid to be aspirated into the airways, triggering an asthma attack, also known as gastric asthma.

Detailed Description

The present invention lessens the problems associated with administration of an NK-1 antagonist, an H_2 antagonist, or a proton pump inhibitor alone and/or provides a means for potentially obtaining a therapeutic effect that is significantly greater than that otherwise obtainable with the single agents when administered alone.

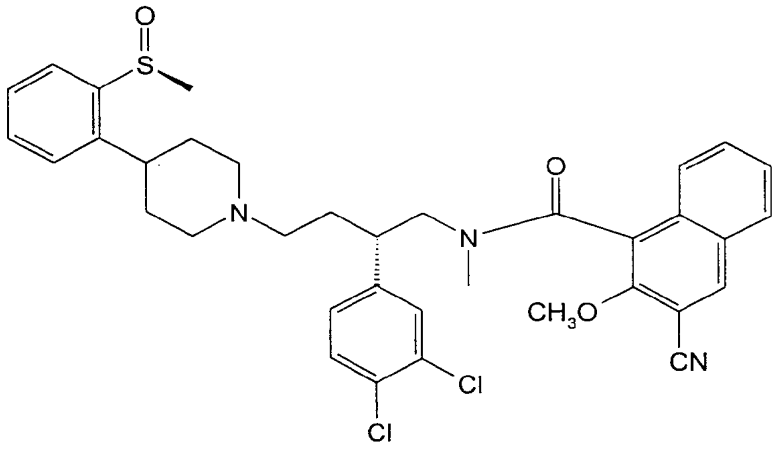
Accordingly, the present invention provides novel combinations, which comprise an NK-1 antagonist and a proton pump inhibitor; or an NK-1 antagonist and an H_2 antagonist; or an NK-1 antagonist, an H_2 antagonist and a proton pump inhibitor.

Additionally, the present invention provides pharmaceutical compositions, which comprise an NK-1 antagonist and a proton pump inhibitor; or an NK-1 antagonist and an H_2 antagonist; or an NK-1 antagonist, an H_2 antagonist and a proton pump inhibitor, together with a pharmaceutically-acceptable carrier and/or diluent.

Another aspect of the invention relates to a method for treating disease related to the reflux of gastric acid in the gastrointestinal system, comprising the step of administering a therapeutically-effective amount of the one of the aforementioned combinations.

Another aspect of the invention relates to the use of one of the aforementioned combinations for the manufacture of a medicament for the treatment of disease related to the reflux of gastric acid in the gastrointestinal system.

Suitable NK-1 antagonists useful in the compositions of the present invention include any compound capable of acting as an antagonist for the neurokinin-1 receptor, for example, those disclosed in United States Letters Patent Nos. 5,521,199, 5,534,525, 5,567,700, 5,576,333, 5,589,489, 5,602,138, 5,635,509, 5,654,299, 5,710,169, 5,731,309, 5,780,466, 5,576,317 and international applications WO 96/24582, WO 97/19060, WO 98/24447, WO 98/47513, WO 98/04561, WO 96/23787, WO 97/13514, EP 98/0302747 or pharmaceutically acceptable salts thereof. Preferred NK-1 antagonist include, for example:



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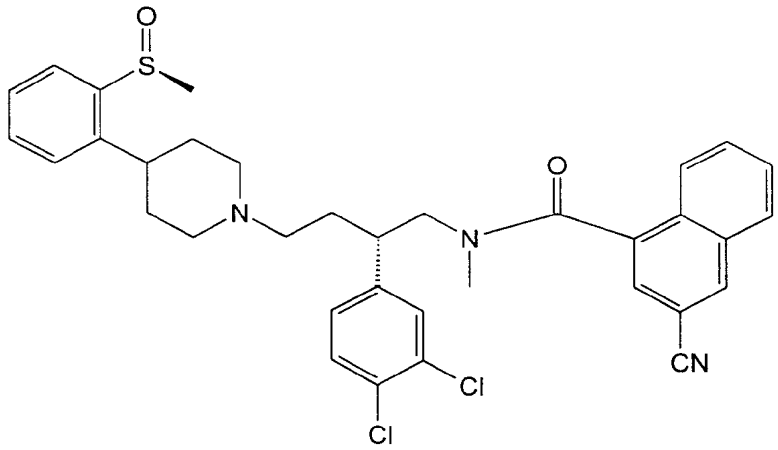

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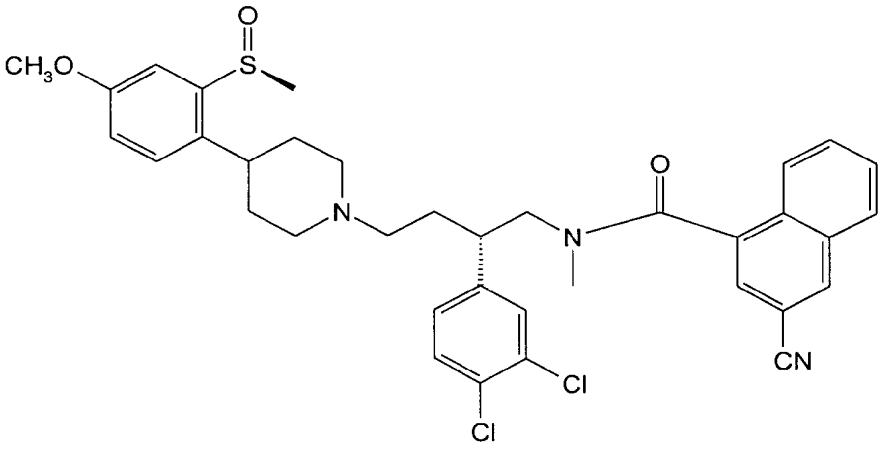

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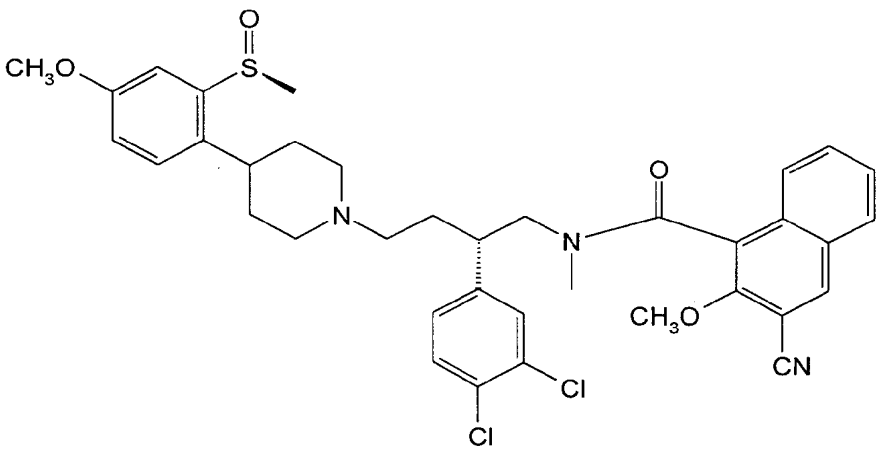

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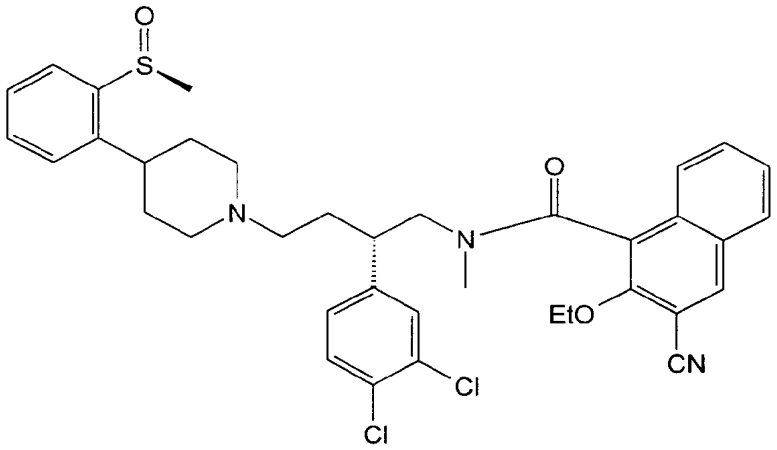

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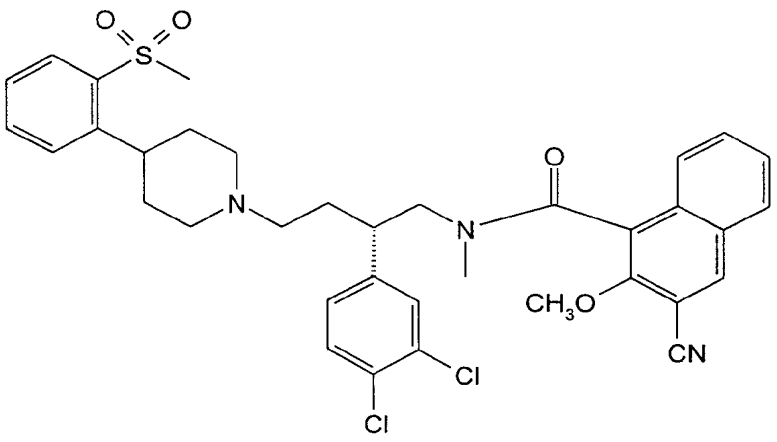

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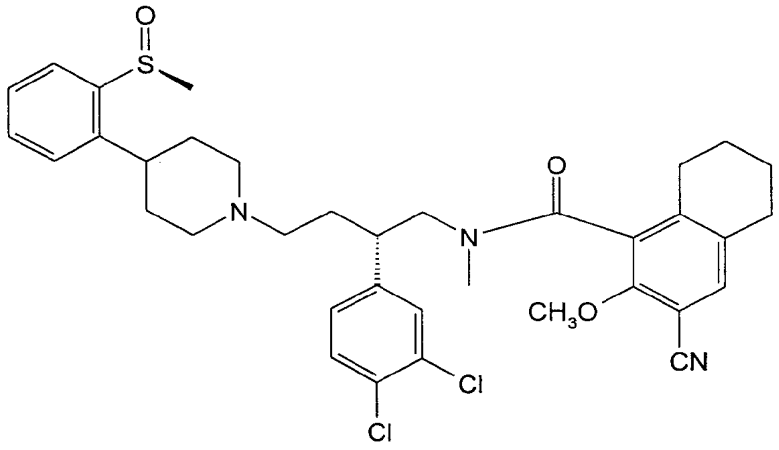

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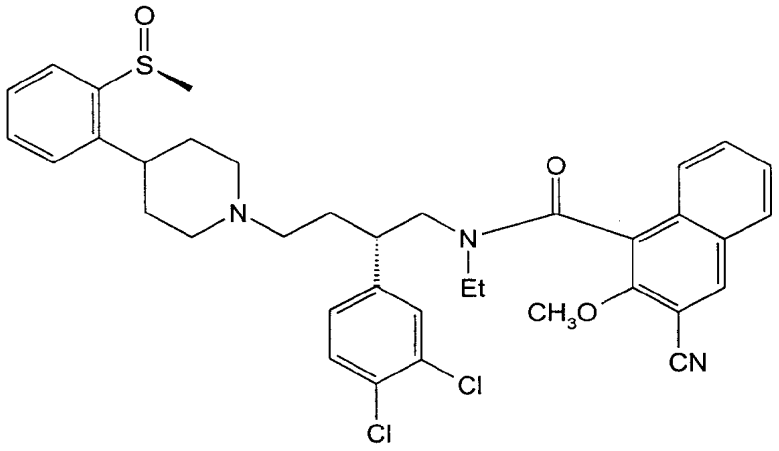

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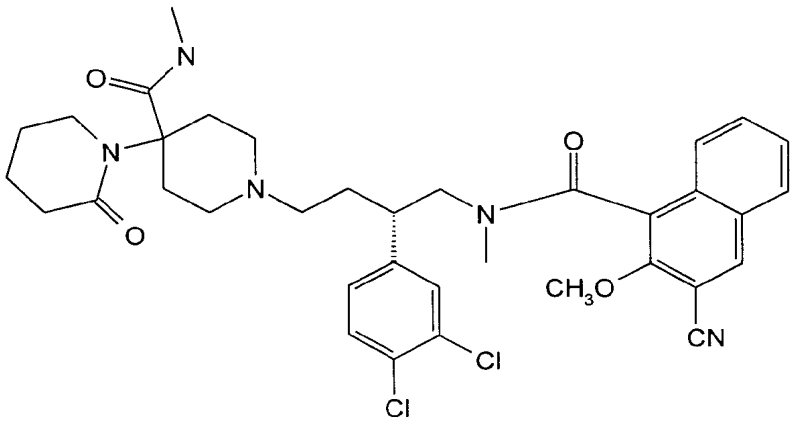

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Other NK-1 antagonists may be identified by the following assays:

SP Receptor Binding Assay (Test A)

The ability of a compound of the invention to antagonize the binding of SP at the NK_1 receptor may be demonstrated using an assay using the human NK_1 receptor expressed in Mouse Erythroleukemia (MEL) cells. The human NK_1 receptor was isolated and characterized as described in: B. Hopkins, et al. "Isolation and characterization of the human

lung NK_1 receptor cDNA" Biochem. Biophys. Res. Comm., 1991, 180, 1110-1117; and the NK_1 receptor was expressed in Mouse Erythroleukemia (MEL) cells using a procedure similar to that described in the Neurokinin A (NKA) receptor binding assay below.

Neurokinin A (NKA) Receptor Binding Assay (Test B)

The ability of a compound of the invention to antagonize the binding of NKA at the NK_2 receptor may be demonstrated using an assay using the human NK_2 receptor expressed in Mouse Erythroleukemia (MEL) cells, as described in: Aharony, D., et al. "Isolation and Pharmacological Characterization of a Hampster Neurokinin A Receptor cDNA" Molecular Pharmacology, 1994, 45, 9-19.

The selectivity of a compound for binding at the NK_1 and the NK_2 receptors may be shown by determining its binding at other receptors using standard assays, for example, one using a tritiated derivative of NKB in a tissue preparation selective for NK_3 receptors. In general, the compounds of the invention which were tested demonstrated statistically significant binding activity in Test A and Test B with a K_i of 1 mM or much less typically being measured.

Rabbit Pulmonary Artery: NK_1 in vitro Functional Assay (Test C)

The ability of a compound of the invention to antagonize the action of the agonist Ac-[Arg^6, Sar^9, $Met(O_2)^{11}$] Substance P (6-11), ASMSP, in a pulmonary tissue may be demonstrated as follows.

Male New Zealand white rabbits are euthanized via i.v. injection into the ear vein with 60 mg/kg Nembutal (50 mg/mL). Preceding the Nembutal into the vein is Heparin (1000 units/mL) at 0.0025 mL/kg for anticoagulant purposes. The chest cavity is opened from the top of the rib cage to the sternum and the heart, lungs and part of the trachea are removed. The pulmonary arteries are isolated from the rest of the tissues and cut in half to serve as pairs.

The segments are suspended between stainless steel stirrups, so as not to remove any of the endothelium, and placed in water-jacketed (37.0 °C) tissue baths containing physiological salt solution of the following composition (mM): NaCl, 118.0; KCl, 4.7; $CaCl_2$, 1.8; $MgCl_2$, 0.54; NaH_2PO_4, 1.0; $NaHCO_3$, 25.0; glucose, 11.0; indomethacin, 0.005 (to inhibit cyclooxygenase); and *dl*-Propranolol, 0.001(to block β receptors); gassed continuously with 95% O_2-5% CO_2. Responses are measured on a Grass polygraph via Grass FT-03 transducers.

Initial tension placed on each tissue is 2 grams, which is maintained throughout the 1.0 hour equilibration period. Tissues are washed with the physiological salt solution at 15 minute intervals. At the 30 and 45 minute wash the following treatments are added: 1×10^{-6} M Thiorphan (to block E.C.3.4.24.11), 3×10^{-8} M (S)-N-[2-(3,4-dichlorophenyl)-4-[4-(2-oxoperhydropyrimidin-1-yl)piperidino]butyl]-N-methylbenzamide (to block NK_2 receptors), and the given concentration of the compound being tested. At the end of the 1.0 h equilibration, 3×10^{-6} M Phenylephrine hydrochloride is added for 1.0 h. At the end of 1.0 h, a dose relaxation curve to ASMSP is done. Each tissue is treated as a individual and is considered finished when it fails to relax further for 2 consecutive doses. When a tissue is complete, 1×10^{-3} M Papaverine is added for maximum relaxation.

Percent inhibition is determined when a tested compound produces a statistically significant ($p < 0.05$) reduction of the total relaxation which is calculated using the total relaxation of the Papaverine as 100%. Potencies of the compounds are determined by calculating the apparent dissociation constants (K_B) for each concentration tested using the standard equation:

$$KB = [\text{antagonist}] / (\text{dose ratio} - 1)$$

where dose ratio = antilog[(agonist -log molar EC_{50} without compound) - (-log molar EC_{50} with compound)]. The K_B values may be converted to the negative logarithms and expressed as -log molar KB (i.e. pK_B). For this evaluation, complete concentration-response curves for agonist obtained in the absence and presence of the compound tested using paired pulmonary artery rings. The potency of the agonist is determined at 50% of its own maximum relaxation in each curve. The EC_{50} values are converted to negative logarithms and expressed as -log molar EC_{50}.

NK-1 antagonists useful in this invention are those that are capable of exhibiting a pK_B value of greater than 7.0 in the Rabbit Pulmonary Artery Assay described above.

Pharmaceutically-acceptable salts of the NK-1 antagonist, in accordance with the present invention, are the salts with physiologically-acceptable bases and/or acids well known to those skilled in the art of pharmaceutical technique. Suitable salts with physiologically-acceptable bases include, for example, alkali metal and alkaline earth metal salts, such as sodium, potassium, calcium and magnesium salts, and ammonium salts and salts with suitable organic bases, such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine and triethanolamine. Suitable salts with physiologically-acceptable acids include, for

example, salts with inorganic acids such as hydrohalides (especially hydrochlorides or hydrobromides), sulphates and phosphates, and salts with organic acids.

Suitable proton pump inhibitors useful in the compositions of the present invention include any compound known to inhibit the gastric acid pump in the stomach. Examples of such compounds include omeprazole, S-omeprazole, rabeprazole, lansoprazole, pantoprazole and leminoprazole, or pharmaceutically-acceptable salts thereof. Preferred proton pump inhibitors include omeprazole, (5-methoxy-2-([(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl)-1H-benzimidazole) and S-omeprazole, or pharmaceutically-acceptable salts thereof.

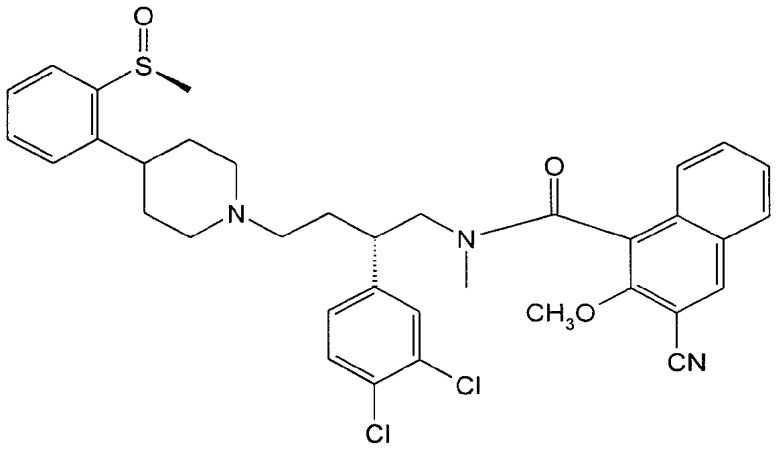
A suitable salt of the proton pump inhibitor omeprazole, or S-omeprazole according to the invention is an alkaline pharmaceutically-acceptable salt. Examples of such salts include inorganic salts, such as alkali metal salts, e.g., sodium salt, potassium salt, etc., alkaline earth metal salts, e.g., calcium salt, magnesium salt, etc., ammonium salt, organic salts such as organic amine salts, e.g., trimethylamine salt, triethylamine salt, pyridine salt, procaine acid, picoline salt, dicyclohexylamine salt, N,N-dibenzylethylenediamine salt, N-methylglucamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)methane salt, phenylethylbenzylamine salt, and dibenzylethylenediamine salt.

The proton pump inhibitors used in the present invention are known compounds in the art, and methods for their preparation may be found in the literature. For example, omeprazole is disclosed in EP 5129, lansoprazole in EP 174,726, pantoprazole in EP 166,287, leminoprazole in GB 2,163,747 and WO 94/27988 describes certain salts of the (-)-enantiomer of omeprazole.

Examples of H_2 antagonists are found in U.S. Patent Nos. 5,889,033, 5,656,652, 5,629,026, 5,622,980, 5,538,737, 5,374,641, 5,273,984, 5,229,418, 5,229,137, 5,221,688, 4,900,741, 4,894,372, 4,847,264, 4,808,589, 4,806,548, 4,788,184, 4,758,576, 4,749,790, 4,738,969, 4,732,980, 4,705,683, 4,694,008, 4,663,331, 4,652,572, 4,636,498, 4,632,927, 4,624,956, 4,622,402, 4,621,142, 4,620,001, 4,608,380, 4,607,107, 4,587,345, 4,574,126, 4,571,398, 4,567,179, 4,567,176, 4,551,466, 4,547,512, 4,540,699, 4,539,316, 4,522,943, 4,503,051, 4,492,794, 4,477,663, 4,466,970, 4,458,077, 4,452,985, 4,450,161, 4,447,611, 4,443,613, 4,439,609, 4,439,437, 4,388,317, 4,385,058, 4,383,115, 4,377,522, 4,359,466, 4,339,439, 4,307,104, 4,279,906, 4,279,819, 4,255,440, 4,230,717, 4,128,658, 4,090,026, however, one of ordinary skill in the art would recognize that other compounds capable of H_2 antagonism would be useful in combination with an NK-1 antagonist.

A preferred pharmaceutical composition of the invention comprises an NK-1 antagonist, or a pharmaceutically-acceptable salt thereof, and a proton pump inhibitor (including any of the proton pump inhibitors specifically named above), together with a pharmaceutically-acceptable carrier and/or diluent.

An especially preferred pharmaceutical composition of the invention comprises the NK-1 antagonist,



or a pharmaceutically acceptable salt thereof, and the proton pump inhibitor omeprazole, S-omeprazole, or a pharmaceutically-acceptable salt thereof, together with a pharmaceutically-acceptable diluent and/or carrier.

The pharmaceutical compositions of the present invention may be administered in standard manner, for example, by oral or parenteral administration, using conventional systemic dosage forms, such as a tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions, or sterile injectable aqueous or oily solutions or suspensions. These dosage forms will include the necessary carrier material, excipient, lubricant, buffer, bulking agent, anti-oxidant, dispersant or the like. In particular, compositions for oral administration are preferred.

The doses of an NK-1 antagonist and a proton pump inhibitor which can be administered in accordance with the present invention depends on several factors, for example, the age, weight and the severity of the condition under treatment, as well as the route of administration, dosage form and regimen, and the desired result, and additionally the potency of the particular NK-1 antagonist and proton pump inhibitor employed in the composition. In addition, account should be taken of the recommended maximum daily dosages for the proton pump inhibitors.

A unit dosage formulation such as a tablet or capsule will usually contain, for example, from 1 mg to 1000 mg of an NK-1 antagonists inhibitor and from 1 mg to 80 mg of a proton pump inhibitor. Another embodiment of a dosage formulation will contain 1 to 500 mg of NK-1 antagonist and 1 to 40 mg of a proton pump inhibitor. Another embodiment of a dosage formulation will contain 10 to 400 mg of NK-1 antagonist and 5 to 20 mg of a proton pump inhibitor.

The pharmaceutical compositions of the present invention may be administered up to two times daily and preferably once a day, so that a dose of the NK-1 antagonist in the general range of 1 to 2000 mg/kg, preferably 1 to 1000 mg/kg, more preferably 1 to 500 mg/kg, is administered daily and a dose of proton pump inhibitor in the general range 1 to 40 mg/kg, preferably 1 to 20 mg/kg, more preferably 1 to 10 mg/kg, is administered daily.

The present invention covers the combination of an NK-1 antagonist and a proton pump inhibitor for simultaneous, separate or sequential use in the treatment of complications related to hypersecretion of gastric acid. In one aspect of the present invention, the NK-1 antagonist or a pharmaceutically-acceptable salt thereof and a proton pump inhibitor or a pharmaceutically acceptable salt thereof are presented in admixture in one pharmaceutical dosage form. In another aspect, the present invention covers the administration of separate unit dosages of the NK-1 antagonist and the proton pump inhibitor in order to achieve the desired therapeutic effect. Such separate unit dosages may be administered concurrently or sequentially as determined by the experienced clinician. Preferably the NK-1 antagonists and the proton pump inhibitor are both administered orally.

In another aspect of the invention there is provided a combination of pharmaceutical compositions for combination therapy of selected GERD complications, the combination consisting of pharmaceutical compositions comprising an NK-1 antagonist and a proton pump inhibitor, wherein the selected GERD complications are heartburn and esophagitis.

A further aspect of the present invention comprises the use of an NK-1 antagonist and a proton pump inhibitor in the preparation of a pharmaceutical composition for use in the treatment of gastric ulcer complications.

A further aspect of the present invention comprises the use of an NK-1 antagonist and a proton pump inhibitor in the preparation of a pharmaceutical composition for use in the treatment of gastric asthma complications.

A further aspect of the present invention comprises the use of an NK-1 antagonist and a proton pump inhibitor in the preparation of a pharmaceutical composition for use in the treatment of duodenal ulcer complications.

A further aspect of the present invention comprises the use of an NK-1 antagonist and a proton pump inhibitor in the preparation of a pharmaceutical composition for use in the treatment of pathological hypersecretory complications.

A further aspect of the present invention is a method for treating complications due to hypersecretion of gastric acid wherein a therapeutically-effective amount of an NK-1 antagonist in combination with a proton pump inhibitor is administered systemically, such as orally or parenterally.

Usually, the proton pump inhibitor will preferably be administered in amounts below that required to cause a reduction in the pH of the contents of the stomach. Where the patient to be treated suffers from pathological hypersecretion, the proton pump inhibitor will preferably be used in greater amounts, e.g. 40 to 100 mg/day. The present invention provides a novel method for treating hypersecretory complications and the amounts of NK-1 antagonist and proton pump inhibitor required when administered in association with the combined therapy are lower than would normally be used, and thus, any deleterious effects or side effects are minimized.

The effect of a pharmaceutical composition of the present invention may be examined by using one or more of the published models of hypersecretory complications well known in the art. The pharmaceutical compositions of the present invention are particularly useful for the prevention of, reducing the development of, or reversal of, deficits in gastric acid secretion found in hypersecretory patients.

Some of the active compounds, especially some proton pump inhibitors, may be susceptible to degradation/transformation in acidic and neutral media. The degradation is catalyzed by acidic compounds and is stabilized in mixtures with alkaline compounds. The stability of the active substances may also affected by moisture, heat, organic solvents and to some degree by light.

In respect to the stability properties of an acid-susceptable proton pump inhibitor, it is obvious that an oral solid dosage form must be protected from contact with the acidic gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

A pharmaceutical oral dosage form of such proton pump inhibitors is best protected from contact with acidic gastric juice by an enteric coating layer. In US-A 4,853,230 such an enteric coated preparation is described. Said preparation contains an alkaline core comprising an acidic susceptible substance, a separating layer and an enteric coating layer. In order to further enhance the stability during storage the prepared formulation may optionally be packed with a desiccant.

A good mechanical stability can be obtained with an enteric coating layered tablet. WO95/01783 describes such a tablet comprising the acid labile compound omeprazole. However, only an enteric coating layered multiple unit tablet can be made divisible and dispersible. A further advantage of a multiple unit dosage form is that it disperses into a multitude of small units in the stomach upon administration.

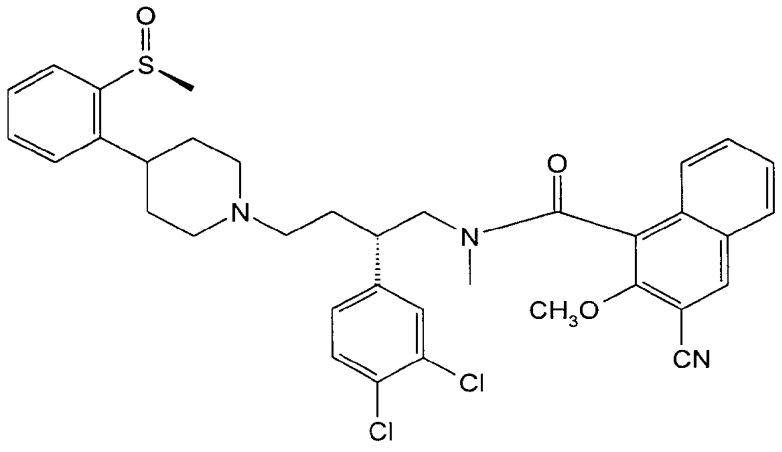
WO 96/01624 discloses tablets comprising enteric coating layered units containing an acid labile proton pump inhibitor or one of its single enantiomers or an alkaline salt thereof can be manufactured by compressing said units into tablets without significantly affecting the properties of the enteric coating layer.

WO 96/01623 discloses tablets comprising enteric coating layered units containing an acidic susceptible substance in the form of omeprazole or one of its single enantiomers, such as S-omeprazole, or an alkaline salt thereof.

Suitable pharmaceutical formulations for proton pump inhibitors are also described in US 4,786,505, US 5,817,338, and 5,753,265, hereby incorporated by reference.

Example

A patient suffering from GERD is treated with a combination of omeprazole (20 mg) Prilosec (tradename) and an NK-1 antagonist (400 mg) having the structure:



CLAIMS:

1. A combination comprising an NK-1 antagonist and an agent capable of reducing the pH of gastric juice in the gut.

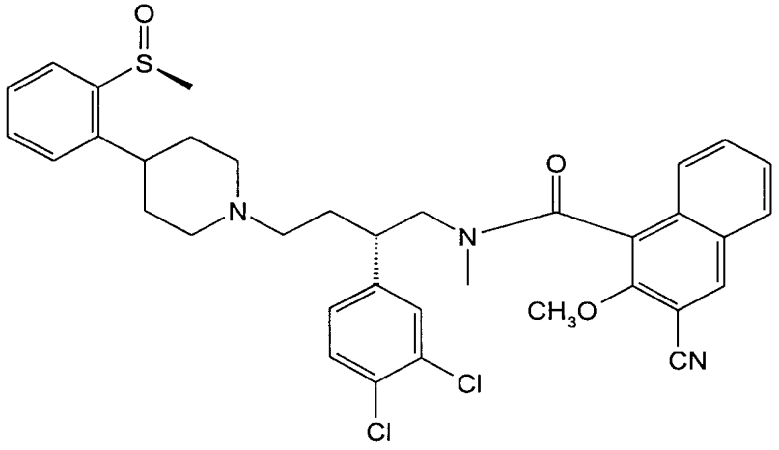
2. The combination according to Claim 1, wherein the agent is a proton pump inhibitor.

3. The combination according to Claim 1, wherein the agent is selected from omeprazole, S-omeprazole, rabeprazole, lansoprazole, pantoprazole and leminoprazole; or a pharmaceutically-acceptable salt thereof.

4. A combination according to Claim 1, wherein the agent is an H_2 antagonist.

5. A combination according to Claim 1, wherein the NK-1 antagonist is any NK-1 antagonist that is capable of exhibiting a pK_B value of greater than 7.0 in the Rabbit Pulmonary Artery Assay.

6. A combination according to Claim 1, wherein the NK-1 antagonist is selected from:



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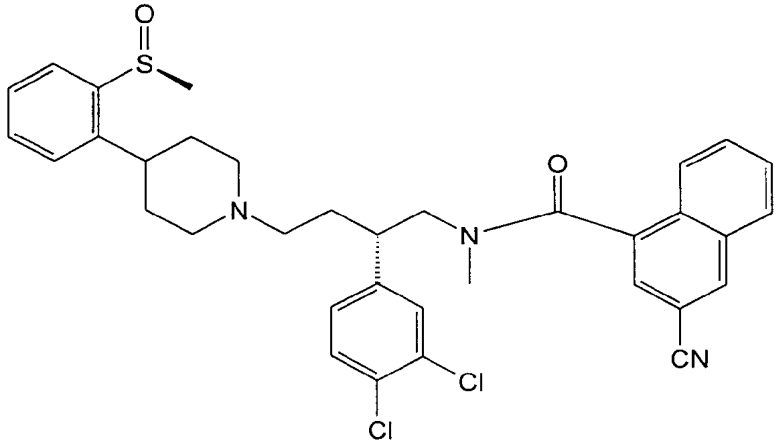

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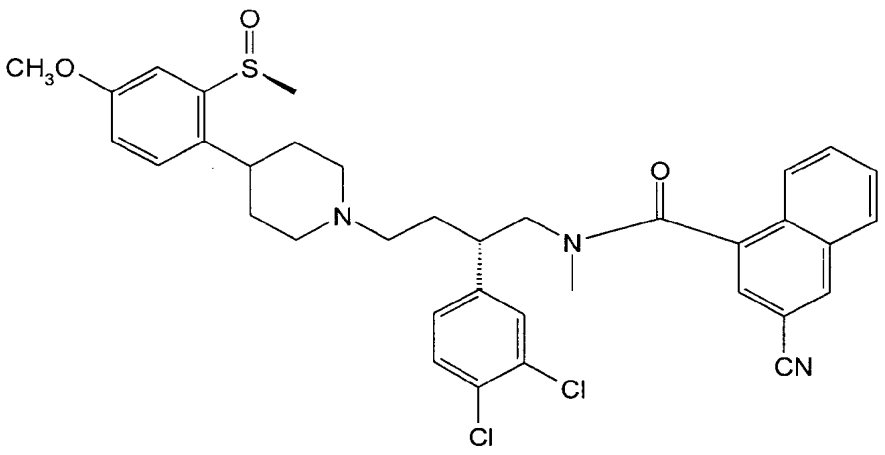

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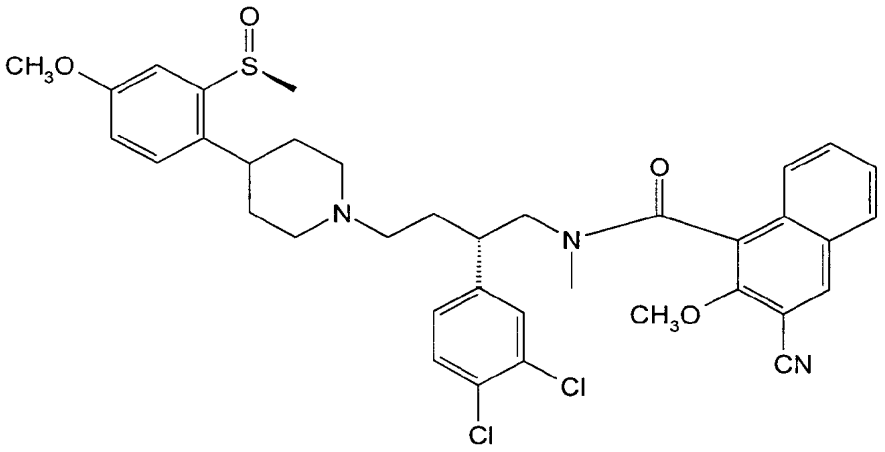

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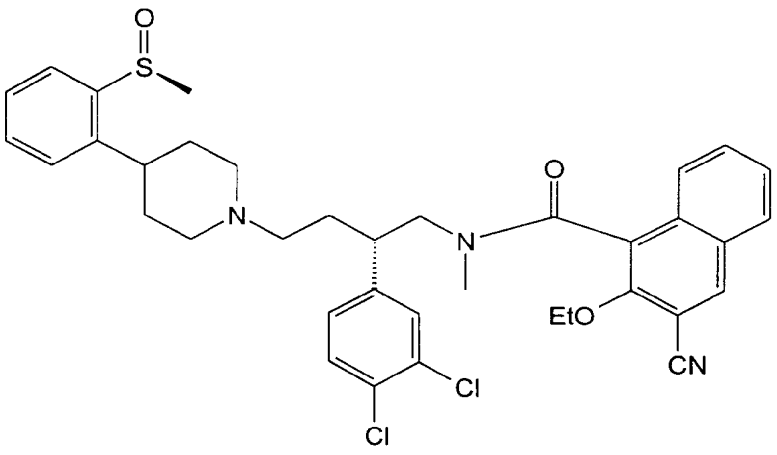

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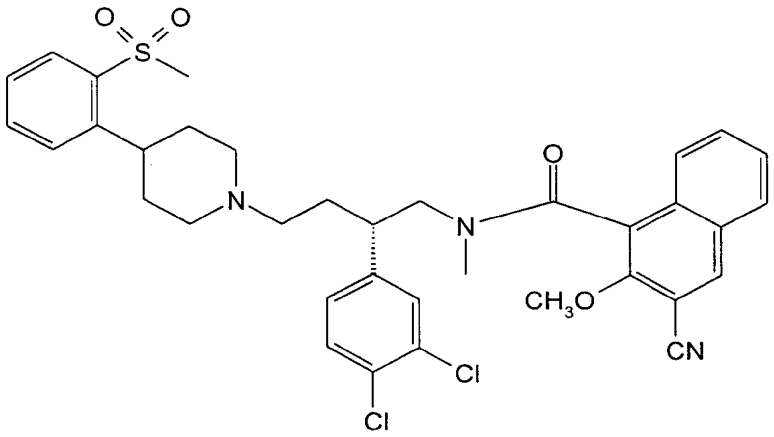

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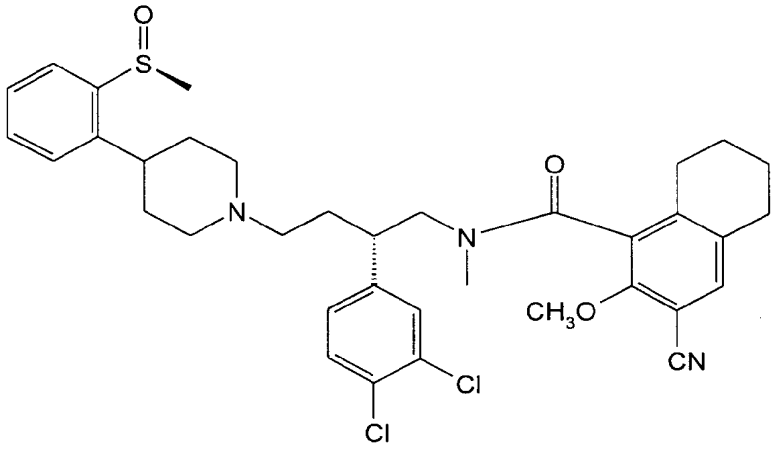

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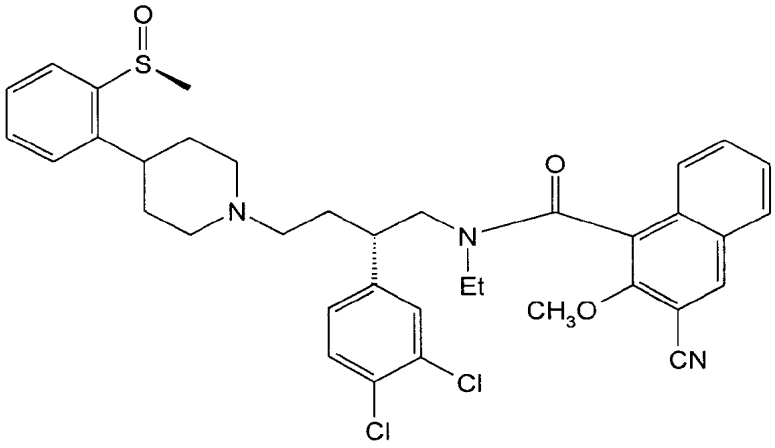

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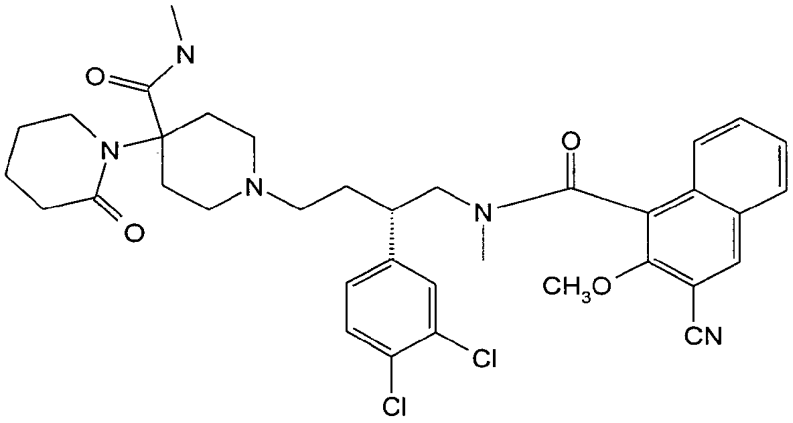

7. A pharmaceutical composition, comprising:

an NK-1 antagonist;

an agent capable of reducing the pH of gastric juice in the gut; and

and a pharmaceutically acceptable carrier or diluent.

8. The pharmaceutical composition according to Claim 7, wherein the agent is a proton pump inhibitor.

9. The pharmaceutical composition according to Claim 7, wherein the agent is selected from omeprazole, S-omeprazole, rabeprazole, lansoprazole, pantoprazole and leminoprazole.

10. A combination according to Claim 7, wherein the agent is an H_2 antagonist.

11. A method for treating disease related to the reflux of gastric acid in the gastrointestinal system, comprising the step of administering a therapeutically-effective amount of a combination according to any one of Claims 1, 2, 3 or 4.

12. The method according to Claim 11, wherein the disease is selected from, heartburn, esophagitis, gastric ulcer, gastric asthma, duodenal ulcer or pathological hypersecretory complications.

13. The use of a combination according to any one of Claims 1 through 4 for the manufacture of a medicament for the treatment of disease related to the reflux of gastric acid in the gastrointestinal system.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 00/01775

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, WPI Data, PAJ, MEDLINE, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"Treatment of gastroesophageal reflux disease" THERAPEUTICS LETTER, 'Online! vol. 3, 1994, XP002145877 Retrieved from the Internet: <URL:www.ti.ubc.ca/pages/letter3.html> 'retrieved on 2000-08-25! abstract ---	1-13
P,Y	HARDING S M: "GASTROESOPHAGEAL REFLUX AND ASTHMA: INSIGHT INTO THE ASSOCIATION" JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY,US,MOSBY - YEARLY BOOK, INC, vol. 104, no. 2, August 1999 (1999-08), pages 251-259, XP000913686 ISSN: 0091-6749 see conclusion page 255, column 1 --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 August 2000	13/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gonzalez Ramon, N

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	STEIN M.R.: "Advances in the approach to gastroesophageal reflux (GER) and asthma." JOURNAL OF ASTHMA, (1999) 36/4 (309-314). , XP000937433 page 311, column 2 -page 312	1-13
A	HALL J.A. ET AL: "Diagnosis and treatment of gastric motility disorders." VETERINARY CLINICS OF NORTH AMERICA - SMALL ANIMAL PRACTICE, (1999) 29/2 (377-395). , XP000900801 page 387 -page 391	1-13
T	CROWELL M.D.: "Editorial overview: Neurogastroenterology: Integration of central and peripheral nervous systems in disorders of GI function." CURRENT OPINION IN CENTRAL AND PERIPHERAL NERVOUS SYSTEM INVESTIGATIONAL DRUGS, (2000) 2/3 (326-328). , XP000937400 abstract page 327, paragraph 2	1-13
P,Y	US 6 013 680 A (KARIYA KINYA ET AL) 11 January 2000 (2000-01-11) abstract; claims 1,4,5	1-13
P,Y	WO 99 59612 A (APHTON CORP ;GEVAS PHILIP C (US); GRIMES STEPHEN (US); KARR STEPHE) 25 November 1999 (1999-11-25) abstract; claims 4-6,8-10	1-13
P,Y	EP 0 968 720 A (AMANO PHARMA CO LTD) 5 January 2000 (2000-01-05) abstract; claim 3	1-13
A	EP 0 426 479 A (MCNEIL PPC INC) 8 May 1991 (1991-05-08) abstract; claim 3	1-13
A	WO 93 12817 A (WARNER LAMBERT CO) 8 July 1993 (1993-07-08) page 6 -page 7; claims 1,5,8	1-13
E	WO 00 25766 A (ZENECA LTD ;LENGEL DAVID JOHN (US); RUMSEY WILLIAM LEROY (US)) 11 May 2000 (2000-05-11) abstract; claims 6,7 page 5, line 12-30	1-13

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INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/GB 00/01775

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 34243 A (ASTRAZENECA UK LTD ;OHNMACHT CYRUS JOHN (US)) 15 June 2000 (2000-06-15) formula II page 7 page 18, line 18-32	1-13

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-13

Present claims 1-13. relate to compounds/compositions defined by reference to desirable characteristics or properties, namely: "a Neurokinin-1 (NK-1) antagonist", "an agent capable of reducing the pH of gastric juice in the gut", "a proton pump inhibitor", "an H2 antagonist". The claims cover all compounds/compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds/compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in the examples and those specifically mentioned in claims 3, 6, 9, with due regard to the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/GB 00/01775

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